The Predictive Value of Exercise Testing and Invasive Assessment Post-Myocardial Infarction Following Treatment with Thrombolysis

A Thesis Submitted to the University of Glasgow for the Degree of Doctor of Medicine

by

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THE PREDICTIVE VALUE OF EXERCISE TESTING AND INVASIVE ASSESSMENT POST MYOCARDIAL INFARCTION FOLLOWING TREATMENT WITH THROMBOLYSIS
SUMMARY FOR EXAMINERS

Introduction

The introductory chapters describe the use of thrombolytic therapy in the treatment of myocardial infarction and discuss the usefulness of exercise testing post-myocardial infarction in the pre and post-thrombolytic eras.

Methods

Two hundred and twelve patients were recruited from four separate studies of thrombolytic agents carried out at Stobhill General Hospital between 1988 and 1993. Patients with symptoms of myocardial infarction lasting > 30 mins and < 6 hrs with diagnostic ST segment elevation on 12 lead ECG between the ages of 18 and 75 years were recruited to our studies if they fulfilled the entry and exclusion criteria.

Coronary angiography was performed at 90 mins and 24 hrs post thrombolysis to define the patency of the infarct-related vessel by the TIMI scoring system (Grades 0-3), additional vessel disease and residual stenosis of the infarct-related artery (≥ 50% stenosis taken as being significant). Prior to discharge from hospital, the patients underwent a symptom-limited treadmill exercise test using a modified Bruce protocol. Symptoms of angina, breathlessness, fatigue or other limiting symptoms were recorded. ST segment depression of ≥ 1 mm, 80 m.secs after the J point was considered indicative of reversible ischaemia. ST segment elevation and T wave normalisation were also recorded and the exercise test was discontinued if there was a significant fall of ≥ 20 mmHg in systolic blood pressure in the previous stage of the exercise test or if the patient achieved age predicted maximum heart rate. Total exercise time in seconds and metabolic equivalents at peak exercise were noted. Systolic blood pressure and heart rate were used to calculate rate pressure product.

When discharged from hospital patients were then followed up for a variable period of time at the outpatient clinics of one of the three Consultant Cardiologists. After approximately 5 years, the case record forms were analysed retrospectively to determine clinical outcome. Cardiac events were noted at three time points: in-hospital cardiac events occurring after angiography at 90 mins to discharge from hospital, outpatient cardiac events occurring from hospital discharge to the end of outpatient follow up, and overall cardiac events which combined both inpatient and outpatient events. Primary cardiac events were defined as unstable angina, recurrent myocardial infarction, PTCA, CABG and sudden cardiac death. Other secondary endpoints were also recorded: peri-infarct acute left ventricular failure, congestive cardiac failure and post-infarct angina.

Statistical Analysis

Minitab software package was used to analyse categorical variables using chi.squared and continuous variables using Anova. SPSS software package was used to perform Kaplan-Meier event-free survival analysis to determine predictive value of univariates. Finally, a multivariate analysis using Cox proportional hazard model was performed using SPSS to determine independent predictors of clinical outcome. In all statistical tests, a significant level of $P < 0.05$ was defined as significant.

Results

Demographic Characteristics

Patients > the median age of 56 yrs were shown to have a higher incidence of cardiac events as an outpatient ($p = 0.0054$) also to have a greater mortality over the 5 year period ($p = 0.023$). Males were significantly more likely to complain of symptoms during exercise compared to females (40% vs 17%, $P < 0.05$). The RCA was affected in 47%, the LAD at 45% and Cx in 7% of patients. ST segment depression during exercise was more common in patients who had had RCA thrombosis. ST segment elevation occurred more commonly in patients with LAD as the infarct-related artery. Patients with LAD as the infarct-related vessel had an increased incidence of acute peri-infarct left ventricular failure ($p=0.029$), chronic heart failure as an outpatient ($p=0.0136$) and the development of heart failure overall ($p=0.03$). As LAD occlusion commonly presents as an anterior infarct, similar results were obtained when comparing site of infarct.

Reciprocal depression defined as significant ST segment depression 80 m.secs after the J point in the non-infarct territory on the admission ECG was associated with ST segment depression during exercise testing, a greater incidence of post-infarct ischaemic pain and peri-infarct left ventricular failure.

Exercise variables: exercise capacity, systolic blood pressure, rate pressure product, ST segment depression, ST segment elevation, T wave normalisation were not associated with results of invasive assessment post-thrombolysis or predictive of clinical outcome.

In this study, failure to undergo an exercise test, for whatever reason, predicted total mortality, but not cardiac events specifically. Angina during exercise testing pre-discharge was predictive of development of angina during outpatient follow up.

Patency of the infarct-related vessel as defined by TIMI scoring did not predict results of exercise testing pre-discharge. Failure to achieve coronary patency with thrombolysis was predictive of post-infarct ischaemic pain as an inpatient, of acute peri-infarct left ventricular failure, chronic heart failure as an outpatient and overall heart failure. Full patency (TIMI Grade 3) and early coronary patency were associated with improved clinical outcome.

Residual stenosis of the infarct-related artery in patients with single vessel or multivessel disease failed to predict results of exercise test or clinical outcome. Patients with three vessel coronary disease were shown to have an increased incidence of ST segment depression during exercise testing and an increased incidence of sudden cardiac death.

Conclusions and Clinical Relevance

Exercise testing pre-discharge in the pre-thrombolytic era was shown to be predictive of clinical outcome and coronary anatomy. Widespread use of thrombolysis in the treatment of acute myocardial infarction has resulted in potential differences in coronary artery anatomy. If a coronary artery is occluded by a thrombosis, this will result in necrosis of myocardial muscle and a variable degree of left ventricular dysfunction. The results of exercise testing and clinical outcome was therefore dependent upon the amount

of myocardial damage and the presence of additional vessel disease. Thrombolysis, by achieving reperfusion of the infarct-related artery in around 60-80% of cases results in myocardial salvage. A residual stenosis of the infarct-related artery exists in around 70% of patients. If this subtends an area of viable myocardium, there is additional reason for reversible ischaemia during exercise testing. Therefore, it is not surprising that non-invasive exercise variables no longer carry the same predictive value as suggested by studies in the pre-thrombolytic area. As thrombolysis results in an improved prognosis following myocardial infarction, any test designed to predict adverse clinical outcome will have a reduced positive predictive accuracy. This present study confirms reduction in the predictive value of a positive test but shows retained negative predictive accuracy in exercise testing post-myocardial infraction in the thrombolytic era. Therefore patients with a normal exercise test following thrombolysis for acute myocardial infarction are at very low risk of future cardiac events and can safely be discharged from hospital follow up. However, it is likely that patients who have significant symptoms of angina post-infarct or a grossly abnormal exercise test will be considered for early invasive investigation with a view to intervention. There remains a group of patients with an abnormal exercise tests result, whose prognosis cannot be defined. They require clinical follow up for a period of time to monitor the course of their symptoms and exercise response before embarking upon invasive investigation.

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DECLARATION

This thesis describes research undertaken during my appointment as the Pfizer Research Fellow located within the Department of Materia Medica, Stobhill General Hospital and, thereafter the Department of Cardiology, Western Infirmary.

I have been fortunate in having the co-operation and collaboration of a number of colleagues who have been formally acknowledged. This thesis is the product of several years research in the field of Thrombolysis. At any one time, three Consultants, three middle-grade Cardiology staff performed 24 hr on-call rota to take part in the thrombolytic studies describedherein. I was involved in recruiting patients for the studies of acute angiography following thrombolysis and subsequent investigations such as exercise testing on the patients.

This thesis concentrates on the relationship between invasive assessment and results of exercise testing post-myocardial infarction following thrombolysis and the prediction of clinical outcome. I personally performed the majority of the exercise tests analysed in this study and was solely responsible for their analysis, also for the analysis of case records to establish cardiac event data. By to use Minitab and SPSS software packages, I personally carried out all the statistical analysis. The writing of this thesis has been entirely my own work. A list of papers presented to the learned societies arising from this work are given in Appendix VIII.

ACKNOWLEDGEMENTS

During my period of research and in the submission of this thesis I have been fortunate in having the advice and collaboration of several colleagues.

Firstly, I should like to thank Professor W Stewart Hillis for recruiting me to Cardiology as the Pfizer Research Fellow. He stimulated my interest in thrombolysis and also encouraged my own interest in exercise, and provided the resources, enabling this research. His enthusiasm, encouragement and helpful discussions sustained the work of this thesis over the 5 year period since its inception.

I am also very grateful to Dr FG Dunn and Dr AP Rae, Consultant Cardiologists at Stobhill Hospital who were an integral part of the thrombolysis team, together with various Registrars in Cardiology. I also thank Kate Howie and, latterly Lilian Murray for providing expert statistical advice which enabled me to perform comprehensive analysis of data. The assistance of Allison McKenzie our research ECG technician who entered the data to spreadsheet format was also much appreciated. Dr Ian Hutton provided an independent score for the coronary angiograms arising from the thrombolytic studies is also gratefully acknowledged. Also, I am indebted to Mrs Jacky Clark for the arduous word-processing of this thesis.

The major part of this thesis concerns exercise testing post-myocardial infarction was carried out by me personally, except where stated. The database used arises from a large patient pool which has been part of the active thrombolysis research programme conducted in Stobhill Hospital. Lastly I wish to formally acknowledge the co-operation of the Coronary Care Nursing Staff, the ECG Department.

1. THE USE OF THROMBOLYTIC THERAPY IN THE TREATMENT OF MYOCARDIAL INFARCTION

1.1 Thromblytic Agents

In this study three thrombolytic agents were used in four separate studies in the treatment of acute myocardial infarction: streptokinase, anistreplase and tissue plasminogen activator. Although other thrombolytic agents exist, they were not in widespread use and therefore not be reviewed in this thesis.

1.1.1 Streptokinase

Streptokinase is a single chain protein produced by group C beta-haemolytic streptococci with a molecular weight of 47000 daltons. It combines with plasmin or plasminogen to form a complex which activates the conversion of plasminogen to plasmin. Streptokinase is a foreign protein and is therefore antigenic. Antibodies in the circulation which have resulted from streptococcus exposure can therefore bind to Streptokinase molecules and neutralise the thrombolytic effects. Streptokinase itself will induce the formation of anti-streptococcal antibodies and thus can reduce the efficacy of subsequent treatment with streptokinase. Lee HS et al. (1993) showed significant antibody levels five days after administration of streptokinase which persisted for up to three years. This obviously has practical implications in terms of the thrombolytic agents used in recurrent myocardial infarction following initial treatment with streptokinase. There is a small incidence of anaphylaxis of approximately 0.1% following administration of streptokinase. Some centres routinely administer chlorpheniramine and hydrocortisone prophylactically to prevent allergic reactions with streptokinase. This treatment is empirical as the evidence to support its effectiveness is lacking (Murray N et al. 1986). Although the administration of streptokinase exerts a hypotensive effect this does not commonly prevent infusion of the standard 1.5 MU dose of streptokinase.

Several large clinical trials have now demonstrated that streptokinase is effective and safe in the treatment of myocardial infarction. It is relatively inexpensive (around £200 for 1.5 million units) and remains the most widely used thrombolytic agent in the

treatment of myocardial infarction in the UK. It is usually dissolved in 500mls of normal saline and given as a continuous infusion. over 1 hour.

1.1.2 Anistreplase

Anistreplase is an anisolated plasminogen streptokinase complex. The active serine site on the plasminogen molecule is anisolated with P-anisoic acid which inhibits the effects of circulating plasmin inhibitors such as alpha-2 anti-plasmin and alpha-2 macroglobulin. Anistreplase undergoes deacylation by hydrolysis to form a potent plasminogen activator, thus exerting a fibrinolytic effect. Anistreplase is a derivative of streptokinase and therefore has similar immunological and haemodynamic effects. However it has the advantage that the standard dose of 30 units of anistreplase can be administered by a single intravenous injection over 5 minutes. Hogg KJ et al. (1990) showed no difference in the efficacy of 30 units of anistreplase compared to 1.5 MU streptokinase assessed by coronary artery patency rates at 90 min and 24 hrs post thrombolysis. The ease of administration of anistrepelase and usefulness in out-of-hospital thrombolysis, particularly in rural settings is a potential advantage of the drug. It is relatively expensive at around £500 for the standard dose.

1.1.3 Tissue Plasminogen Activators

Tissue Plasminogen Activators were identified as serine proteases by Astrup T and Permin PM in 1947. However at that time they could not be obtained in sufficient quantity from human tissue for experimental purposes. Tissue plasminogen activators were then isolated and purified from a melanoma cell line (Collen D et al. 1982). The gene involved in the synthesis of tPA was then cloned and expressed it in ***E coli*** allowing the production of recombinant tissue type plasminogen activator (r-tPA) in quantities which allowed evaluation in humans (Pennica D et al. 1983).

As a human protein tPA is not antigenic and is therefore not associated with allergic reactions caused by streptokinase containing compounds. It has been shown to exert minor hypotensive effects (Lew AS et al. 1995). It has a short half-life, around five minutes (Garabedian DH et al. 1987) and therefore, its systemic effects are relatively short-lived. The ability of r-tPA to cause lysis of a coronary thrombosis was first

demonstrated by Van der Werf F et al. (1984). Six out of seven patients given r-TPA achieved coronary reperfusion without depletion of fibrinogen, plasminogen or alpha-2 antiplasmin However, it has since been shown that doses of tissue plasminogen activator required to provide satisfactory coronary reperfusion rates did cause a significant fall in fibrinogen and plasminogen, thus exerting a systemic lytic effect (Rao AK et al. 1988). This is now thought to be an advantage in preventing early coronary reocclusion, a problem encountered with lower doses. R-tPA exists in two forms: the initial form of rTPA was a double-stranded preparation **DUTEPLASE** but subsequently a single-stranded chain version **ALTEPLASE** was developed which had higher specific activity and was easier to produce in quantity (Garabedian DH et al. 1987).

Although r-tPA is less antigenic and better tolerated than streptokinase-containing compounds, it is relatively more expensive (around £600 per 100mg). However, in patients who have previously been treated with streptokinase, tPA is the drug of choice for treatment of recurrent myocardial infarction in some clinical centres. Following streptokinase it takes approximately 5 days to achieve significant antibody levels. Therefore in clinical practise redosing with streptokinase would be recommended within this five day period. Several studies have shown that significant antibody levels persist up to 3 years after administration of streptokinase. Thus re-dosing with streptokinase at any point after five days for recurrent myocardial infarction is becoming less common. The standard regime of r-tPA at present is 100mg of alteplase as a 3 hour decremental intravenous infusion. The short-lived systemic effects of TPA and its ease of administration as an intravenous bolus have stimulated a variety of studies considing different dose regimes in an attempt to define the most effective. Neuhaus KL et al. (1989). showed improved efficacy with administration of TPA in an accelerated regime: 15mg bolus IV followed by infusion of 50mg over 30 min and then 35mg over 1hr

1.2 Historical Review of Thrombolysis

Tillet WS and Sherry S in 1949 used Streptokinase to dissolve fibrinous material *in vitro*. The lysis of intravenous blood clots in rabbits by streptokinase was then demonstrated by Johnson A J et al. (1952). Administration of intravenous and intracoronary thrombin was shown to lyse thrombotic occlusions in dog coronary

arteries by Ruegsegger et al. (1959). A sustained systemic lytic state in 22 patients with acute myocardial infarction was demonstrated following administration of streptokinase (Fletcher AP et al. 1959). No serious haemorrhagic complications were encountered.

The first large scale controlled trial in thrombolysis comparing streptokinase with heparin was conducted in 558 patients treated within 12 hours of the onset of symptoms for acute myocardial infarction (Schmutzler N et al. 1966). Following a loading dose of streptokinase, an infusion was given for 18 hours with a variable dose regime designed to maintain a thrombolytic state. A significant improvement in mortality was shown in the streptokinase treated group, (14.1% v 21.7 % at 40 days, $p<0.01$). This benefit of streptokinase was confirmed in a further 269 patients treated within 6 hrs of onset of symptoms of myocardial infarction with a loading dose of 250,000 units followed by 167,000 units per hour for 18 hours against placebo (Schmutzler N et al. 1971). The 40 day mortality of the streptokinase treated group was 14.5% v 26% for the placebo group, ($p<0.01$). In addition, there was an improvement in the 24 hr mortality rate (2% v 10%, $p<0.001$).

In 1969 the first European Working Party trial was published with 167 patients treated within 72 hours of the onset of symptoms of myocardial infarction with either heparin or streptokinase (1.25 MU loading dose and 104,000 U/hr for 72 hours) (Amery A et al. 1969). Those patients treated with streptokinase in fact had a significantly higher mortality rate possibly explained by a 72-hour inclusion time.

In 1971, the second European Working Party trial recruited 730 patients within 24 hours of onset of symptoms for acute myocardial infarction in a randomised double-blind study of streptokinase (250,000 U loading dose followed by 100,000 U/hr for 24 hours) or heparin(European Working Party, 1971). At 40 days mortality in the streptokinase group was 18.5% compared to 26.3% in the heparin group ($p<0.01$).

However, in a study of 321 patients treated within 12 hours of symptoms it was shown that the treatment group who received 250,000 U of streptokinase as a loading dose followed by 1,500 U/hr for 12 hours did not have significant improvement in mortality

compared to the control group treated with heparin (Dioguardi N et al. 1971). Similarly, in a study of 747 patients treated with streptokinase (250,000 loading dose and 1,000 U/hr for 18 hours) did not have improved survival over a control group treated with heparin (Bett JHN et al. 1977).

Aber CP et al. (1976) showed no difference in mortality at hospital discharge in a group of 595 patients within 24 hours of the onset of symptoms of myocardial infarction randomised to receive 2.5 MU of streptokinase v placebo (12.6% v 13.7%). Similarly at 6 months there was no difference in mortality (15.9% v 17.8 %). Therefore, the results of early thrombolysis studies were conflicting in terms of the benefits of streptokinase therapy in acute myocardial infarction.

Several animal experiments demonstrated the ability of streptokinase to achieve reperfusion and result in myocardial salvage, reduction in creatine kinase production, reduction in necrotic histological changes and increased contractility of the myocardium.

Myocardial salvage was shown to be time-dependent in experiments which mechanically occluded coronary arteries in dogs and restored flow at various time points after occlusion (Reimer KA et al. 1977). Reperfusion up to six hours resulted in significant salvage of epicardial myocardium. The study therefore suggested that benefits of thrombolysis given with a view to achieving coronary artery reperfusion may be limited to a similar time window following the onset of symptoms. Therefore, previous studies which administered streptokinase late after the onset of symptoms of myocardial infarction may not demonstrate the true beneficial effects of thrombolysis.

1.2.1 Intracoronary Streptokinase in Acute Myocardial Infarction

In a study of 322 patients admitted within 24 hours of the onset of acute myocardial infarction, 87% of the patients studied by angiography within 4 hours of the onset of symptoms had thrombotic occlusion of the affected coronary artery (DeWood MA et al. 1980). In 88% of patients with angiographic features of coronary thrombosis it was possible to mechanically retrieve thrombus material using a Fogarty catheter. Therefore, the role of coronary thrombosis in the aetiology of myocardial infarction was confirmed.

The rate of spontaneous reperfusion was estimated at 13% at 4 hrs rising to 35% at 12-24 hours.

Forty-one patients were treated with 2,000 U/min of intracoronary streptokinase combined with mechanical reperfusion with a guidewire (Mathey DG et al. 1981). 95 % of the patients had completely occluded coronary arteries. It was possible to obtain reperfusion in 73% of these patients. Repeat coronary angiography at 7-21 days in 15 of the 41 patients showed that 80% of them continued to have patent infarct related arteries.

Other studies confirmed similar reperfusion rates with the use of intracoronary streptokinase, and showed improved left ventricular function in patients with coronary artery patency (Timmis AD et al. 1982; Rentrop P et al. 1981; Ganz W et al. 1981). It was demonstrated by coronary angiography that 78 of 81 patients treated within 3 hours of the onset of myocardial infarction with 0.75 or 1.5 MU of streptokinase over 15-30 mins had patent infarct related vessels at 3-7 days by coronary angiography (Ganz W et al. 1984).

However, other studies, showed similar efficacy of intracoronary streptokinase in achieving coronary artery reperfusion but failed to show any difference in left ventricular ejection fraction measured at 7-10 days (Leiboff RH et al. 1984; Khaja F et al. 1983). Metanalysis of previous studies of streptokinase by Stampfer MJ et al. (1982) using the results of 8 randomised trials of intravenous streptokinase compared to a control group treated with either placebo or heparin. They showed a statistically significant improvement in mortality at 40 days in the streptokinase-treated patients with an overall hazard ratio of 0.8 ($p<0.1$).

Similarly, a metanalysis by Yusuf S et al. (1985)of 33 studies using intravenous and intracoronary thrombolysis in the treatment of acute myocardial infarction calculated an overall hazard ratio of 0.78 and a reduction in mortality of 22% ($p<0.001$) in favour of those patients receiving streptokinase in the 24 trials of intravenous thrombolysis. In 9 studies of intracoronary streptokinase, an average odds ratio of 0.8 and a mortality

reduction of 20% was shown. This did not reach statistical significance, but this may have represented a type II error as there were only 128 deaths out of 1,000 patients considered for analysis.

Although intracoronary administration of thrombolysis allows direct assessment of the thrombotic occlusion of the infarct-related vessel and an instant evaluation of the efficacy of thrombolysis in achieving patency, it does not appear to have significant advantages in improving mortality rate compared to intravenous administration. Coronary angiography is a highly skilled, invasive and expensive procedure which is not available to all physicians in the United Kingdom. Arterial cannulation in patients treated with thrombolysis state is associated with increased bleeding complications because of the induced systemic lytic (Merx W et al. 1981). Even in specialist centres, there is a significant amount of time required to organise coronary angiography which delays the administration of therapy. A study of 28 patients by Alderman EL et al. (1984) randomised to receive intracoronary or intravenous streptokinase confirmed that there was no significant difference in rates of reperfusion (73% v 62%). In addition, there were similar reductions in fibrinogen with intravenous and intracoronary administration despite significantly lower dose administered to the intracoronary route. It was concluded that a systemic lytic state was necessary to achieve successful coronary perfusion rather than high local concentrations of streptokinase. The results were supported by a similar study performed by Rothbard RL et al. (1985).

1.2.2 Assessment Of Thrombolytic Efficacy

1.2.2.1 Coronary Reperfusion

A pre-treatment angiogram must be performed to identify an thrombotic occlusion of the of the infarct related artery. It is then possible to assess whether thrombolytic therapy has achieved lysis of the occlusive thrombus by post treatment angiography. This can be quantified according to the TIMI score developed by Williams DO et al. (1986). The organisation of a pre-treatment angiogram may lead to a significant delay in administration of thrombolysis. Therefore recent studies of intravenous thrombolytic therapies do not assess efficacy in this way.

1.2.2.2 Coronary Patency

To avoid delays in administration of thrombolytic therapy incurred by a pre-treatment angiogram, patency of the infarct related vessel is assessed similarly at some point after administration of therapy. Obviously, the phenomenon of spontaneous reperfusion (around 15-20%) will contribute to patency rates, which will therefore be greater than reperfusion rates and lead to an overestimate of the effectiveness of thrombolytic agents. This can be similarly quantified by the TIMI score

The rate of spontaneous reperfusion and the rate of coronary artery patency following thrombolysis increases with time. A study of 30 U of anistreplase v 1.5 MU streptokinase given intravenously showed that patency increased from around 55% at 90 minutes to around 85% at 24 hours after therapy (Hogg KJ et al. 1990). In addition, from the onset of symptoms of myocardial infarction to therapy affects the patency rate achieved with thrombolysis (Timmis AD et al. 1987).

1.2.2.2.1 Streptokinase

Intracoronary streptokinase reperfusion rates were calculated in the order of 60-87% (Timmis AD et al. 1982) and intravenous streptokinase of around 62% (range 44-75%) (Alderman EL et al. 1984).

1.2.2.2.2 Anistreplase

Coronary artery patency rates with 30 U of anistreplase as a 5 min bolus intravenous injection is in the order of 50-70%. No significant difference in patency rates were shown between anistreplase and streptokinase at 90 minutes (55 v 53 %) or at 24 hours (81 v 87.5 %)(Hogg KJ et al. 1990).

1.2.2.2.3 Tissue Plasminogen Activators

Tissue plasminogen activator exists as duteplase, a double-chain r-tPA and alteplase a single chain version. It is known that the specific activities of these two preparations differ, which may influence the interpretation of results of studies using either agent. In addition, because of the relative ease of IV bolus administration, a variety of dose

regimes of r-TPA have been studied. The specific properties of tPA may be enhanced by dose manipulation and this may affect the validity of comparing results of different studies. A patency rate of around 68% was achieved using 70mg of duteplase over 90 minutes and 80% using 1.5 μg/kg of alteplase over 4 hours in conjunction with heparin (Topol EJ et al. 1987). The TIMI-1 study used 80mg of rTPA over 3 hours with a patency rate of around 56%(The TIMI Study Group, 1987). Accelerated administration of rTPA with a 15mg bolus followed by 50mg over 30 mins and 35mg over 90 mins (a total dose of 100mg) gave increased coronary artery patency of around 74% at 60 mins and 91% at 90 mins(Neuhaus KL et al. 1989). 100mg of rtPA given as 4 x 25mg boluses over 60 minutes achieved patency of the infarct related artery in 11 of 14 patients (Khan MI et al. 1990). There is therefore widely differing reported rates of patency following different regimes and forms of tPA administration.

1.2.3 Preservation of Left Ventricular Function

Thrombolytic therapy results in salvage of a variable amount of myocardium, by restoring blood flow to the infarct zone, and therefore should theoretically reduce left ventricular dysfunction post myocardial infarction. Methods available for assessment of left ventricular function include contrast left ventriculography, echocardiography and radionucleotide ventriculography. Left ventriculography is obviously an invasive procedure performed in addition to a coronary angiogram and therefore has limited potential for serial assessments. Echocardiography, is non-invasive and repeatable. However, a significant number of individuals will have poor quality images which prevent accurate measurements of left ventricular volumes. Radionucelotide angiography is non-invasive and reproducible and can be used for serial measurements of both global and regional LV function, however, this facility may not be readily available in all centres. Left ventricular function has been shown to improve spontaneously up to 2 weeks following myocardial infarction independent of treatment with thrombolytic therapy (Schwarz F et al. 1982) In this study, improvement in LV function correlated with amount of residual flow to the infarct zone, either antegrade or via collateral circulation. Ejection fraction over a 2 week period following infarction was elevated in patients with residual flow in the infarct zone compared those without (Rogers WJ et al. 1984). It was postulated that an initial compensatory hyperkinesis of the non-infarct zone was non-sustained post infarct and resulted in a fall in ejection

fraction. Infarct size was reduced and LV function preserved with i.v. streptokinase but these benefits were confined to those patients with anterior infarction treated within 3 hrs of the onset of symptoms(Ritchie JL et al. 1984).

1.3 Patency Studies

TIMI-1 (The TIMI Study Group, 1987)was a randomised, double-blind angiographic trial comparing 1.5 MIU with streptokinase with 80 mg r-tPA in 290 patients with suspected myocardial infarction. It demonstrated superior earlier patency with r-tPA (62%) compared to streptokinase (31%) ($p<0.01$) at 90 mins. However, a patency rate of 31% for streptokinase is unusually low, compared to most other studies which indicated a patency rate of around 51-64% with 1.5 MIU of i.v. streptokinase (Hogg KJ et al. 1990) and may reflect the design of the study. An uncontrolled angiographic trial of accelerated r-tPA in 80 patients with suspected myocardial infarction demonstrated that r-tPA given as an accelerated regime gave a patency rate of 91% at 90 mins (Neuhaus KL et al. 1989).The RAAMI Study in 1992 was a randomised, open angiographic study comparing accelerated tPA with conventional tPA in 281 patients with a suspected myocardial infarction (The RAAMI Study Group 1992). This showed accelerated tPA had a greater patency rate (76%) than standard r-tPA (63%) at 60 mins ($p<0.003$) but it did not show a significant difference in patency rates at 90 mins (81% vs 77%, p=NS).

The TAPS study (Von Essens R et al. 1991) was a randomised, angiographic trial comparing accelerated r-tPA with 30 U of anistreplase in 421 patients with suspected myocardial infarction. It showed that accelerated tPA had a significantly higher patency rate at 90 mins vs anistreplase (84.4% vs 70.3%, $p=0.0007$) and also a significantly lower in-hospital mortality with accelerated tPA at 2.4% vs 8.1% ($p=0.0095$). However, there was a higher early reocclusion rate (24-48 hrs) with accelerated tPA 10.3% vs 2.5% anistreplase.

The GUSTO study (1993) (The Gusto angiographic invesigators, 1993) had an angiographic sub-study containing 2,431 patients which showed significantly increased rate of patency (TIMI grade 2 or 3) with accelerated tPA at 90 mins ($p<0.001$) and

increased rate of TIMI grade 3 (54%, $p<0.001$). This was independent of age, infarct-related artery and time to therapy. Patients with full patency (TIMI grade 3) at 90 mins were shown to have improved left ventricular function. Mortality rates were also shown to depend upon patency at 90 mins, as shown below in table 1.1. 30 day mortality was also influenced by the number of coronary vessels diseased : a stenosis of $\geq$ 75% as illustrated in table 1.2. The GUSTO study was the first large scale study to link patency at 90 mins with clinical outcome and concluded that thrombolytic regimens which could achieve high early patency rates were of additional benefit, particularly if reocclusion could be prevented

Patency Group	Mortality Rate	P Value
TIMI 0,1	8.9%	
TIMI 2,3	5.7%	**0.004**

Table 1.1 Relationship between patency and mortality in the Gusto Study(The Gusto angiographic invesigators, 1993)

Vessel Diseased	Percentage affected	Mortality	P values		
			No of diseased vessels multiple comparisons		
				1	2
1	62%	3.5%			
2	24%	6.5%	2	0.03	
3	14%	11.2%	3	0.001	0.02

Table 1.2 The no of vessels diseased and mortality in the Gusto Study (The Gusto angiographic invesigators, 1993)

1.4 Mortality Studies

The benefits of thrombolytic agents and the treatment of acute myocardial infarction have been established by the results of several large scale mortality studies.

The GISSI-I study in 1986 was a randomised, open trial of 1.5 MIU streptokinase vs control in 11,806 patients up to 12 hrs after the onset of symptoms of acute myocardial infarction (The GISSI Working Group 1986). There was an 18% reduction in 21 day mortality (10.7 v 13%, $p<0.0002$) with a 10% reduction in mortality at 12 months (17.2 v 19.0%, $p=0.008$). Benefit was shown to be time-related with a 23% reduction in 1 year mortality in patients treated within 3 hrs and a 39% reduction in patients treated within 1 hr. No significant benefit was shown in patients treated after 6 hrs. The incidence of stroke in this study was 0.2%, major bleeds 0.3% and anaphylactic reactions 0.1%, establishing the relative safety of streptokinase administered to a large group.

The ISIS-2 study in 1987 was a randomised, double-blind placebo controlled mortality study of 17,187 patients receiving 1.5 MIU streptokinase, oral aspirin, both or neither for acute myocardial infarction (The ISIS 2 Working Group 1987). The study showed a highly significant benefit in 5 week mortality in patients treated with streptokinase, aspirin and streptokinase plus aspirin vs placebo. The results are summarised below in Table 1.3.

Treatment	Mortality	P Value
Placebo	13.2%	0.001
Aspirin	10.7%	0.001
Streptokinase	10.4%	< 0.0001
Streptokinase + Aspirin	8%	< 0.0001

Table 1.3 Mortality rates with Streptokinase, Aspirin and Placebo from ISIS-2 (The ISIS 2 Working Group 1987

Therefore the effects of streptokinase and aspirin appear to be additive, achieving an overall reduction in mortality of 25%. Those patients treated within 4 hrs of symptoms with streptokinase therefore had a 35% reduction in mortality compared to 16% for

those treated within 5-12 hrs and 21% treated within 13-24 hrs. Those patients receiving streptokinase between 13 and 24 hrs did not have significant improvement in mortality when compared to placebo. In ISIS-2 ECG changes of ST elevation were not applied as entry criteria to the study. However, the sub-group analysis suggested that those patients with normal ECGs or ST depression thought to be clinically experiencing myocardial infarction did not receive significant benefit from thrombolysis.

The TIMI-1 study in 1987 was a randomised double-blind, angiographic study of 290 patients with suspected myocardial infarction comparing 1.5 MIU streptokinase vs 80 mg r-tPA. Patency at 90 min with r-tPA was 62% vs 31% with streptokinase ($p<0.001$) (The TIMI Study Group, 1987). This trial demonstrated the benefits of tPA in achieving early patency, but the numbers were too small to examine mortality.

The ASSET study (Wilcox RG et al. 1990) was a randomised, double-blind, placebo controlled study of 100 mg of r-tPA in 5,011 patients within 5 hrs of onset of the symptoms with suspected myocardial infarction. r-tPA (alteplase) was given in a decremental infusion over 3 hrs and compared against placebo. Mortality in the tPA group at 1 month was 7.2% vs 9.8% in the placebo group. This shows a relative reduction in mortality of 26% ($p=0.011$). The benefits of mortality were maintained at 6 months (relative reduction 21%) and at 1 year (relative reduction 12.6%).

The AIMS study was a randomised, double-blind, placebo controlled trial of 30 U anistreplase in 1,004 patients with suspected myocardial infarction up to 6 hrs after the onset of symptoms (AIMS Trial Study Group. 1988). Diagnostic criteria of ST segment elevation were required for entry into the study. All patients were heparinised followed by warfarin for at least 3 months and received a betablocker (timolol) in the absence of contraindications. There was a relative reduction in mortality of 47% at 30 days and 43% at 1 year in the treated group. This study did not demonstrate improved benefit in those patients treated after 4 hrs.

The benefits of thrombolysis vs placebo was therefore established by the studies described above. Therefore, further placebo controlled trials could not be justified on ethical grounds and the next series of large scale studies looked at the relative benefits of different thrombolytic agents.

The GISSI-2 study was an open, randomised trial of 1.5 MIU streptokinase vs 100 mg tPA (in a standard decremental infusion) in 20,891 patients with suspected acute myocardial infarction. In-hospital mortality was 8.7% and similar within 3 treatment arms (The GISSI Working Group 1988) as shown in table 1.4.

Treatment	Mortality
r-tPA + Heparin	9.2%
Streptokinase	9.2%
Streptokinase + Heparin	7.9%

Table 1.4 Mortality data from GISSI-2 (The GISSI Working Group 1988)

There was no significant difference between the groups. In addition, there was a significant increase in the incidence of strokes in the tPA group compared to streptokinase (1.3% v s 0.9%).

The ISIS-3 study was a randomised, double-blind trial comparing 1.5 MIU streptokinase, anistreplase 30U and r-tPA (duteplase 0.6 MU/kg) in 41,299 patients with suspected myocardial infarction. In addition, each thrombolytic agent was considered with/without the addition of subcutaneous heparin 4 hrs after treatment (The ISIS Working Group 1992). The results showed that there was no significant difference between streptokinase, anistreplase and r-tPA in 5 week mortality rates (10.5, 10.6, 10.3% respectively). There was a significantly lower incidence of stroke in the streptokinase group at 1.1% ($p<0.001$).

The GUSTO study was a randomised, controlled trial, comparing 1.5 MIU streptokinase and accelerated r-tPA in 41,021 patients with suspected myocardial infarction. 30 day mortality in the four treatment groups are shown below(The Gusto invesigators, 1993) in table 1.5.

Treatment	30 Day Mortality
SK + s.c. Heparin	7.2%
SK + i.v. Heparin	7.4%
Accelerated tPA	6.3%
r-tPA + SK + i.v. Heparin	7%

Table 1.5 Mortality data from the Gusto Study (The Gusto Invesigators, 1993)

This showed that r-tPA administered in an accelerated regimen had a significant mortality benefit over streptokinase ($p<0.01$), and also that there was no significant benefit from streptokinase plus r-tPA (1 mg/kg) plus i.v. heparin. However, there was an increased incidence of stroke in the accelerated tPA group but in terms of net clinical benefit which is a composite analysis of 30 day mortality or non disabling stroke, accelerated rtPA still shows significant benefit, table 1.6.

Treatment	Net Clinical Benefit
SK + s.c. Heparin	7.7%
SK + i.v. Heparin	7.9%
SK (pooled results)	7.8%
Accelerated r-tPA	7.9%

Table 1.6 Mortality data from the Gusto study (The Gusto Invesigators, 1993)

2. EXERCISE TESTING AFTER MYOCARDIAL INFARCTION

2.1 Exercise Testing

2.1.1 Historical Perspective

Before 1960 it was common for patients recovering from an acute myocardial infarction to have extended bed rest in hospital and a very gradual resumption of daily activities following discharge. Cain HD et al (1962) used a graded activity programme with ECG monitoring to assess 335 patients recovering from an uncomplicated myocardial infarction Poor exercise capacity was correlated with the development of ST segment depression, ST segment elevation, and multifocal premature ventricular contractions. Torkelson LO, (1964) was first to use a low level exercise test to assess the functional capacity of 10 patients seven weeks post M.I Total exercise time and electrocardiographic changes during exercise were used as the basis for exercise prescription in an individualised comprehensive cardiac rehabilitation programme. In 1971 bicycle ergometry was used to assess ST segment changes occurring during exercise in 12 patients, three weeks after an anterior myocardial infarction (Atterhog JH et al. 1971). In 10 of the 12 patients, ST segment elevation with normalisation of inverted T waves was noted in the leads relating to the site of infarction. In addition, 3 subjects developed pronounced ST segment depression which was attributed to coronary insufficiency. Ibsen H et al. (1975) in a study of 209 patients at a mean of 18 days post M.I. using symptom-limited bicycle ergometry showed that angina or breathlessness occurred as the limiting symptoms in 23% of patients and significant ST segment depression indicative of myocardial ischemia in occurred in 70% of patients.

No complications with early exercise testing post myocardial infarction were reported and it was therefore concluded that the test was safe. As an objective assessment of functional capacity it was also used to prescribe baseline exercise levels in the resumption of daily activity. In 1973 a heart rate limited treadmill test was performed on 100 patients 3 weeks post myocardial infarction (Ericcson M et al. 1973). The occurrence of ventricular ectopic beats during exercise testing was greater, but not statistically significant in those patients who sustained an arrhythmia during the acute phase of myocardial infarction. In addition,

20% of the patients developed angina pectoris during exercise testing and it was concluded that this procedure allowed objective evaluation of the exercise response in each patient. It was therefore essential prior to rehabilitation.

Abnormal symptomatic, electrocardiographic and haemodynamic responses to exercise were described in this patient group and formed the basis for further studies to determine the prognostic significance of these variables.

2.1.2 Type of Exercise Test

An exercise test in the clinical setting should be designed to yield the maximum amount of information regarding the patient's functional capacity and prognosis, with minimal risk. In 1978 the effects of isometric and dynamic exercise were compared in 40 patients, 7 weeks post myocardial infarction (DeBusk RF et al. 1978). Dynamic whole body exercise was superior to isometric exercise in eliciting abnormal electrocardiographic exercise responses. In addition, it was shown that dynamic leg exercise was superior to dynamic arm exercise in assessing patients maximum exercise capacity. This result was supported in a further study by Galbraith et al. (1975) which compared the usefulness of isometric hand grip testing to low level treadmill testing in 55 patients, 3 weeks post myocardial infarction. The isometric hand grip test did not produce an abnormal exercise response in patients post myocardial infarction. The use of treadmill testing was recommended to provide an adequate stimulus to the cardiovascular system to enable the assessment of maximum exercise capacity and elicit responses to physical activity which reflected underlying clinical pathology.

Isometric exercise requires sustained muscle contraction, without change in muscle length. This prevents adequate muscle perfusion by mechanical compression of the vascular supply and may increase total peripheral resistance. Although this results in an increased pressure load on the heart, there is a minimal increase in myocardial oxygen demand with isometric exercise compared to whole body dynamic exercise.

Isometric exercise is achieved by anaerobic metabolism and does not result in the significant increase in muscle blood flow and total body oxygen consumption caused by dynamic exercise.

2.1.3 Intensity of Exercise

Patients recovering from myocardial infarction were previously perceived to be at risk of acute ischemic or arrhythmic events during maximum, symptom-limited exercise testing. It was therefore recommended that they should undergo a low level sub-maximal exercise test in preference. A low level exercise test has defined end-points such as the achievement of a pre-determined heart rate or workload. Heart rate limited tests have been arbitrarily defined as absolute values in the range of 110-130 beats/min or at a given percentage of age-predicted maximum heart rate (200-Age beats/min). Similarly, workload limited low level tests have been defined by the achievement of an exercise level in the range of 3-5 metabolic equivalents. Symptom-limited and heart rate limited exercise testing were compared 3 weeks post myocardial infarction (De Busk RF et al. 1982). The low level exercise test was terminated at a heart rate of 130 beats/min in the absence of limiting symptoms. There was a higher peak heart rate and workload in patients who completed the symptom-limited protocol. However, the incidence of exercise induced ST segment depression and premature ventricular ectopics was not significantly different in the two groups. In both groups of patients, ST segment depression but not premature ventricular ectopic activity was predictive of early cardiac events. The study does not state whether the patients were randomised, and therefore the results may reflect selection bias. However, Starling MR et al. (1981) compared predischarge low level heart rate limit and symptom-limited exercise testing in a crossover study of 29 patients following an uncomplicated myocardial infarction The sequence of the exercise tests was randomised. The symptom-limited exercise test resulted in a significant increase in total exercise time, peak heart rate, peak rate pressure product and maximum workload when compared to the heart rate limited exercise test. The incidence of ST segment depression and angina was significantly greater, in the symptom-limited exercise test.

In 1992 low level and symptom-limited exercise tests were compared by Juneau M et al. before hospital discharge after uncomplicated myocardial infarction. 200 patients were exercised using both protocols in a randomised sequence on consecutive days at a mean of 7.4 $\pm$ 2.3 days after infarction. The symptom-limited protocol achieved a greater exercise duration, peak workload, peak heart rate and rate pressure product. There was a significant increase in the number of patients who exhibited ST segment depression of $\geq$ 1 mm with a symptom-limited exercise test. Differences between the exercise protocol was independent of type of infarction (Q wave versus non-Q wave) or administration of thrombolytic therapy. They concluded the increased cardiovascular stress of a symptom-limited protocol is associated with a greater diagnostic accuracy in terms of exercise-induced ischemia.

2.1.4 Timing of Exercise Testing

The timing of an exercise test following a myocardial infarction may have implications on the safety of the test and its predictive value. In 1979 low level exercise testing prior to discharge was evaluated by Smith JW et al. in 109 patients with uncomplicated myocardial infarction Patients were exercised using a modified Bruce protocol to 60% of the patients age predicted maximum heart rate at a mean of 18 days post myocardial infarction. Patients who developed ST segment depression during exercise had a significantly increased incidence of recurrent ischemic events during a mean follow up period of 21 months. However, the overall number of events in both groups was small and the results of exercise testing led to therapeutic interventions which may have potentially influenced outcome. However, it was demonstrated that early exercise testing post-myocardial infarction was safe and of potential predictive value. Starling MR et al. (1981) used a modified Naughton protocol to compare a symptom-limited exercise test performed pre-discharge and at 6 weeks post-myocardial infarction in 89 patients recovering from uncomplicated myocardial infarction. 9 patients who failed to perform the exercise test at 6 weeks post discharge, because of an early recurrent ischemic event, had abnormal electrocardiographic responses in the pre-discharge exercise test. ST segment depression was highly reproducible in the patients who completed both pre-discharge and 6 weeks post discharge exercise tests. Other abnormal exercise responses such as angina, inadequate rise in systolic blood pressure and

ventricular ectopic activity had limited reproducibility. This study therefore demonstrated that if a symptom-limited exercise test was performed prior to discharge, there was no additional information to be gained from repeating the test at 6 weeks post myocardial infraction.

Senaratne MPJ et al. (1988) compared low level pre-discharge and 6 weeks post discharge symptom-limited exercise testing in a further study of 518 patients and showed that ST segment changes and also symptoms of angina were similar during the low level pre-discharge test and the symptom-limited post discharge test.

In a review by Stang and Lewis (1981) of the early studies in pre-discharge exercise testing it was concluded that exercise testing pre-discharge in low risk patients was safe, but the predictive value of an ischemic response and the indications for intervention remained unclear. The addition of thallium scintigraphy was recommended to enhance the predictive value of exercise testing post- myocardial infarction.

In 1988 it was shown by Topol EJ et al that following an uncomplicated myocardial infarction an exercise test performed at 3 days was safe, feasible and cost-effective. In a group of 179 patients who were exercised and subsequently discharged three days after uncomplicated myocardial infraction it was shown that there was no increased incidence of fatality or recurrent events, compared to control patients who were exercised between 7 and 10 days and then discharged.

2.1.5 Safety of Exercise Testing Post Myocardial Infarction

The studies cited above, confirm the safety of exercise testing post myocardial infarction. None of the studies reported a significant incidence of adverse events. In addition, exercise testing as early as 3 days and the use of a symptom- limited protocol have been shown to be feasible and safe post uncomplicated myocardial infarction.

However, it is difficult to evaluate the overall safety of exercise testing from these studies, as the patients are being carefully selected to fulfil entry criteria and have usually sustained an uncomplicated myocardial infarction and therefore may not represent the true clinical spectrum.

Potential complications of post myocardial infarction exercise testing include myocardial rupture, aneurysm formation, extension of the myocardial infarction or precipitation of lethal arrhythmias (Hamm LF et al. 1986). Two cases of ventricular fibrillation were reported during exercise testing at 4 weeks post myocardial infarction in a total group of 325 patients (Norris RM et al. 1984). In a series of over 1500 patients exercised post myocardial infarction reported a 4% incidence of ventricular arrhythmias requiring termination of the exercise test and 1 fatality from ventricular fibrillation (Pedersen A et al. 1980).

In 1979 concern was raised by Lindsay J, about the safety and usefulness of early exercise testing. They highlighted 1 fatality during exercise testing at 13 days post myocardial infarction which was shown at post mortem to be due to myocardial rupture.

Contraindications to early exercise test post-myocardial infarction were identified (Goldschlager N Sox HC, 1988):

1. Advanced age
2. Chest pain at rest, 2-5 days prior to exercise test
3. Systolic hypertension >150 mmHg
4. Clinical evidence of heart failure
5. Poorly controlled atrial or ventricular arrhythmias
6. Resting ECG changes consistent with myocardial ischemia

The ESC Working Group (1993) guidelines for cardiac exercise testing recommended that early post-infarct angina, severe heart failure and AV conduction abnormalities were contraindications to exercise testing in the post infarct period. These contraindications were used to define a complicated myocardial infarction in its broadest sense. Once medical therapy has been optimised, it may then be desirable to exercise patients with the above conditions to complete the clinical assessment or determine whether invasive investigation is indicated. The clinical significance of abnormal exercise test variables in complicated versus uncomplicated myocardial infarction was studied in 455 patients, 3 weeks post myocardial infarction (Saunamaki KI and Anderson JD, 1987). No deaths were reported during exercise testing in either group. During a 4.5 year follow up period, mortality was 49% in complicated infarcts versus 23% in uncomplicated infarcts. ST segment depression did not predict mortality in either of these clinical groups.

However, the definition of complicated myocardial infraction was relatively non-specific, which included patients with left bundle branch block and patients receiving medications such as Digoxin, betablockers, calcium antagonists and antiarrhythmics.

2.2 Risk Stratification Post Myocardial Infarction

The clinical rationale for risk stratification post myocardial infarction after myocardial infarction is to identify patients at high risk of further ischemic events, life-threatening arrhythmias or sudden death. These patients may benefit from invasive investigation with a view to intervention which may improve prognosis. The clinical course following myocardial infarction and the results of exercise testing have been extensively studied to determine the predictive value of clinical variables and abnormal responses during exercise.

2.2.1 Clinical Variables

In 1984 a study of 205 patients post infarct it was found that a history of previous MI, high CK value and resting ST segment depression were predictive of outcome. The only exercise variable which independently predicted future events in a multivariate analysis was exercise duration (Williams WL et al. 1984). Cripps T et al. (1988) in a study of 176 patients post

infarct found that exercise variables predicted further ischemic events, clinical variables and late potentials on signal averaged ECG predicted future arrhythmia. In the same year, a study of 559 survivors of less than 66 yrs of age used clinical variables and an abnormal exercise test to define a complicated myocardial (Campbell S et al. 1988):

1. Angina 1 month prior to infarction
2. Ventricular arrhythmias
3. Recurrent pain
4. Cardiac Failure or cardiomegaly
5. Abnormal ETT:
   - Angina
   - ST Segment Depression
   - Inadequate BP response

Increased mortality at a median time of 2.4 yrs in patients with complicated compared to those with uncomplicated myocardial infarction (24.6% v 10.2%).. Therefore clinical characteristics such as recurrent myocardial ischemia, common persistent left ventricular dysfunction and significant cardiac arrhythmias identified patients at high risk of sudden death following myocardial infarction. These clinical characteristics were defined as (O'Rourke RA, 1991):

A. Recurrent Myocardial Ischemia

1. Recurrent chest pain after first 24 hours
2. New ST changes on electrocardiogram with/without angina
3. Further elevation of cardiac enzymes

B. Severe left ventricular dysfunction

1. Persistent sinus tachycardia
2. Systolic blood pressure < 90 mmHg
3. Third heart sound
4. Radiographic evidence of pulmonary venous congestion
5. Cardiomegaly

C. Recurrent Arrhythmias

1. Ventricular tachycardia
2. Ventricular fibrillation
3. Asystole
4. New bundle branch block
5. AV conduction abnormalities
6. Atrial tachycardia

Such clinical events define a complicated myocardial infarction with a 15-30% risk of a further myocardial infarction or cardiac death within the first year. Therefore patients in this category, if suitable, should be considered for invasive investigation with a view to early intervention to reduce mortality. Although exercise testing is of value to complete the clinical assessment of patients with complicated myocardial infarction, it is perhaps more useful in assessing patients with uncomplicated myocardial infarction to identify patients with exercise-induced reversible ischemia and other abnormal exercise responses who also require early investigation. Fioretti P et al (1986) showed that clinical variables associated with the development of left ventricular function, dysfunction and significant arrhythmias also identified those patients with an adverse clinical outcome. The mean ejection fraction and radionucleotide ventriculography was strongly associated with survival. Patients who died had a mean ejection fraction of < 30% compared with 43% in those patients who survived.

2.2.2 Predictive Value of Exercise Test Variables

The electrocardiographic and haemodynamic responses to exercise have been extensively investigated in patients post myocardial infarction in an attempt to identify which variables are most sensitive and specific for the identification of patients at high risk of recurrent ischemic events or sudden death. Such patients might benefit from invasive investigation by means of coronary angiography to define their specific coronary artery anatomy, and if indicated, undergo revascularisation by PTCA or CABG.

2.2.2.1 ST segment depression

ST segment depression which occurs during exercise and resolves during the recovery period is termed reversible ischemia. Significant ST segment depression is defined as horizontal or downsloping ≥ 1 mm 80 m.sec after the J point (the junction of the ST segment of the QRS complex) in three consecutive complexes in two contiguous leads. In normal individuals, ST segment depression occurs at high levels of exercise with an appropriate heart rate response. However, the direction of the ST segment is commonly upsloping and does not indicate underlying coronary artery disease. Kentala E, (1976) in a 6 yr follow up study of 158 men post infarct under 65 yrs of age showed an association between early onset ST segment depression and sudden death In an influential study, Theroux et al (1979) investigated 210 patients with uncomplicated myocardial infarction with a low level exercise test at a mean of 11 days post infarct. They found patients who had ST segment depression during exercise testing post myocardial infarction had a 27% mortality at 1 year compared to a 2.1% 1 year mortality rate in those without ST segment depression. ST segment depression predicted mortality but not other ischemic events such as unstable angina, myocardial infarction or post-infarct angina during the follow up year. The study was the first to show an association between abnormal exercise test variables and mortality in post-infarct patients. However, the authors included patients with sub-endocardial myocardial infarction (n=37) which is now known to represent a different clinical entity with an altered short term prognosis. The authors did not perform subgroup analysis of Q wave versus non-Q wave infarction. The result of the exercise test did not influence therapeutic decisions or the indications for invasive investigation. Five percent of

patients who underwent coronary artery bypass surgery were referred for invasive investigation on clinical grounds. In this study medical treatment was prescribed on clinical grounds and not on the basis of the presence of ST segment depression or other exercise test variables. In addition, a further analysis removing patients receiving Propranolol and Digitalis still showed an increased mortality in patients with ST segment depression (22% versus 2.6%). Fifteen patients developed ST segment elevation during exercise and were excluded on this basis from the analysis. This electrocardiographic response is not thought to represent reversible ischemia and therefore could still have been included in the analysis of the group who did not develop ST segment depression. Table 2.1 below shows the cardiac event rate in patients with either angina, ST segment depression or both during the exercise test.

Coronary Events	No Angina or ST↓	Angina Alone	ST↓ Alone	Angina + ST↓
None	70	2	10	1
Angina	45	10	15	18
(CABG)	(5)	(1)	(1)	(5)
Unstable Angina	4	0	1	1
Myocardial infarction	8	4	1	0
Death	3	0	10	7
Total	130	16	37	27

Table 2.1 Cardiac event rate in patients with either angina, ST segment depression or both during the exercise test (modified from Theroux 1979)

Coronary artery bypass surgery but not stable angina would be considered as hard ischemic end point in follow up of patients post myocardial infarction. A reanalysis of the data from Theroux et al 1979 is presented in Table 2.2

Coronary Events	No ST ↓	ST ↓
None	72	11
Unstable Angina	4	2
Myocardial Infarction	12	1
Death	3	17
Total Events ($X^2 = 50.361$, $P < 0.001$)	25	26

Table 2.2 The incidence of cardiac events excluding angina in patients with ST segment depression (modified from Theroux 1979)

Further calculations were performed to derive 2 x 2 contingency tables to consider total events and death in relation to ST segment depression during exercise. This is shown in Tables 2.3 and table 2.4.

Coronary Events	No ST↓	ST ↓
No Event	72	11
Events ($X^2 = 22.495$, $p < 0.001$)	25	26

Table 2.3 Total events in relation to ST segment depression during exercise.

This shows that patients who experienced ST segment depression during exercise had a significantly greater increased cardiac event rate in the follow up period of 1 year.

Coronary Deaths	No ST ↓	ST ↓
No Death	143	47
Death ($X^2 = 31.015$, $p < 0.001$)	3	17

Table 2.4 Coronary death in relation to ST segment depression during exercise

As shown above, ST segment depression during exercise identifies patients at risk of death in the first year. From this analysis of data from Theroux et al, sensitivity, specificity, predictive accuracy of the positive test and the predictive accuracy of the negative test were calculated for all cardiac events combined and death. This is summarised in Table 2.5.

	All Cardiac event ST↓s	Death ST↓
Sensitivity	41%	50%
Specificity	76%	80%
Predictive Accuracy of +ve Test	50%	50%
Predictive Accuracy of -ve Test	80%	90%

Table 2.5 The predictive value of exercise testing

As shown, ST segment depression and angina have low sensitivity and poor positive predictive accuracy. However, the test is relatively specific and there is very good predictive accuracy of a negative result. Therefore patients with no ST segment depression during exercise have an excellent prognosis. In addition angina during the follow up period in the absence of other cardiac events was considered an ischemic end point. If angina preceding unstable angina, recurrent myocardial infarction or cardiac death had be considered as a secondary independent end point then the prediction of post infarct angina from the exercise test may have been improved. Chi squared tests were used in the analysis of the data which does not take the timing of an event or the loss of follow up into account. Kaplan Meier Survival analysis would have perhaps been a more appropriate statistical method and there was no attempt at multivariate analysis. However, this paper was the first to clearly establish a relationship between ST segment depression during exercise testing post myocardial infarction and mortality at 1 year. The design of the study, which allowed therapeutic or surgical interventions only on clinical grounds and not on the results of the exercise test, increased the impact of their observations within the existing literature.

Further studies Belder M et al. (1988) supported these results. In a group of 262 survivors of acute myocardial infarction, those with an abnormal exercise test response pre-discharge were 13 times more likely to die in the first year. They defined an abnormal exercise test response as :

1. angina pectoris
2. ST segment depression horizontal or downsloping ≥ 1 mm,
3. an inadequate systolic blood pressure response
4. dyspnoea or fatigue
5. frequent ventricular extrasystoles.

In addition, those with an abnormal response to exercise were three times more likely to have an ischemic event and twice as likely to develop left ventricular failure than those with a normal exercise response post infarct. A study of 195 men undergoing post infarct exercise testing showed that in a multivariate analysis ST segment depression of ≥ 2 mm was predictor of further cardiac events (Davidson MD and DeBusk RF, 1980). However, clinical and exercise variables in 259 male patients following a myocardial infarction were studied to determine which variables predicted a poor prognosis (Sanz G et al. 1982). In a univariate analysis they found that the only predictors of survival were ejection fraction ≤ 50% and the number of diseased vessels at coronary angiography performed at 4 weeks post myocardial infarction. They did not find that abnormal exercise test variables predicted mortality in this group of patients during a mean follow up period of 34 months. However, the exercise test post myocardial infarction was not performed until 6 months. Deaths and other cardiac events occurring within this period of time could not be included in the analysis which may have altered the predictive value of the test.

The relative value of clinical variables, bicycle ergometry, resting nucleotide ventriculography and 24 hour ambulatory electrocardiographic monitoring, were to predict

one year mortality in a group of 351 survivors of myocardial infarction (Fioretti P et al. 1986). It was concluded that the development of ST segment depression or angina during the exercise test did not have a significant predictive value. The results were unchanged when the patients who underwent revascularisation were excluded from the analysis. Similarly it was shown that ST segment depression in lead 5 during exercise testing was not significantly associated with increased risk of death in the first year (Jennings K et al. 1984) or long-term prognosis, in 54 patients followed for 9 years post infarction (Nielsen JR et al. 1990).In a meta-analysis by Jespersen C M et al. (1993) of 12 studies from 1979-1989 in which the predictive value of exercise testing in patients recovering from myocardial infarction was assessed, ST segment depression of ≥ 1mm was shown to significantly increase the risk of sudden death or reinfarction with an overall odds ratio of 1.90 (CI 1.43,2.51). ST segment depression in inferior and non q wave infarcts compared to q wave anterior infarcts was shown to improve risk assessment. Anterior infarcts were more commonly associated with heart failure which was strongly associated with adverse outcome. and there was reduced sensitivity of ST depression in combination with anterior infarcts.

2.2.2.2 ST Segment Elevation

The significance of ST segment elevation during exercise remains unclear. It usually occurs in the exercise ECG in the leads showing sequential changes following a Q wave myocardial infarction. It is thought to represent an exercise induced wall motion abnormality rather than reversible ischemia. A study of 74 patients in 1984 undergoing low level exercise testing at a mean of 9.7 days following acute myocardial infarction showed that ST elevation, ST depression or both were predictors of subsequent cardiac events including cardiac death, left ventricular failure, recurrent myocardial infarction and angina during 11.3 months of follow up when compared with patients with normal exercise test responses (Sullivan ID et al. 1979). Further multivariate analysis showed that ST segment elevation was the only independent variable which predicted cardiac death. A significant association was shown between the development of ventricular arrhythmias and exercise induced ST segment elevation (Belder M et al. 1988). However other studies showed that

ST segment elevation during exercise testing at a mean of 14 days in 407 survivors of myocardial infarction, did not predict clinical outcome (Fioretti P et al. 1986) and no significant differences were found between survivors and non survivors of myocardial infarction who developed ST elevation during exercise (Nielsen JR et al. 1990). It is likely that ST segment elevation during exercise represents a wall motion abnormality of the infarct site and has a complex relationship with exercise ejection fraction (Sanz G et al. 1982).

2.2.2.3 Angina Pectoris

The development of angina pectoris during the pre-discharge exercise testing post myocardial infarction has been shown by some authors to be predictive of future fatal and non fatal cardiac events. The original study by Theroux et al (1979) found that 65% of patients who developed angina pectoris during exercise testing developed stable angina in the follow up year. Re-analysis of this data presented above, excluding post infarct angina as a ischemic event shows that angina during the exercise test predicted cardiac events but not death as shown in tables 2.6-2.9.

Coronary Events	No angina	Angina
None	134	25
CABG	6	6
Unstable Angina	5	1
Myocardial Infarction	9	4
Death	13	7
Total Events	33	18

Table 2.6 Angina during exercise testing in the prediction of coronary events other than post infarct angina (modified from Theroux 1979).

Coronary Events	No Angina	Angina
No Events	134	25
Events($X^2 = 9.08$, $p < 0.05$)	33	18

Table 2.7 Angina during exercise testing in the prediction of all coronary events combined other than post infarct angina (modified from Theroux 1979).

Coronary Deaths	No Angina	Angina
No Deaths	154	36
Death($X^2 = 2.84$, p = NS)	13	7

Table 2.8 Angina during exercise testing in the prediction of coronary deaths (modified from Theroux 1979).

	All Cardiac Events	Death
Sensitivity	31%	35%
Specificity	79%	81%
Predictive Accuracy of +ve Test	31%	16%
Predictive Accuracy of -ve Test	80%	90%

Table 2.9 Angina During exercise in the prediction of all cardiac events and sudden death (modified from Theroux 1979).

Angina during exercise testing post infarct does predict future cardiac events. The absence of angina identifies patients at low risk post infarct. It was reported that angina pectoris reported during exercise testing was predictive of future coronary artery bypass surgery within 2 years of follow up, in 195 men following uncomplicated myocardial infarction (Davidson MD and DeBusk RF, 1980). However, it failed to show any relationship between the development of angina during exercise testing and further cardiac events such as recurrent myocardial infarction and sudden death.

A study by Starling MR et al. (1981). reported that angina associated with ST segment depression or an inadequate systolic blood pressure response was predictive of all cardiac events during a mean follow up period of 11 months A further study in 1982 in a group of 188 patients recovering from an uncomplicated myocardial infarction, showed that those who experienced angina during the pre-discharge exercise test at a mean of 10 days had a significantly increased incidence of recurrent myocardial infarction during a 27 month period of follow up (Jelinek VM et al. 1982). In a study of 184 males of less than 55 yrs, angina during the exercise test, but not ST segment depression was shown to predict angina and the need for CABG in the follow up period for 1 yr (Peart I et al. 1989). In a study of 867 patients post myocardial infarction the 33% of patients with early angina (including predischarge exercise test) had a greater incidence of cardiac admissions and CABG but no increase in overall mortality at 1 or 4 yrs (Benhorin J et al. 1988). A further study showed no difference in mortality, left ventricular function, lipid profile or type of infarct (q wave v non q wave) in those patients with or without angina during exercise testing. Angina was significantly more common in patients defined as having a positive exercise test result (≥ 1mm ST↓) (30% v 8%,p,0.0001)(Karnegis JN et al. 1982).

2.2.2.4 Ventricular Ectopic Beats

In a symptom-limited exercise test 3 weeks post myocardial infarction in 317 patients multifocal ventricular ectopic activity was a predictor of cardiac death during a mean follow up period of 5.7 years (Saunamaki KI and Anderson JD, 1982).However in Debacker G, (1982). in a review of the prognostic significance of ventricular ectopic activity during exercise testing post M.I. It was concluded that ventricular ectopic activity was common, occurring in over 50% of patients, but that the predictive value was not fully established with the majority of existing studies failing to show ventricular ectopic activity as an independent predictor of morbidity and mortality However, the study reported that ventricular ectopic activity correlates with impaired left ventricular function which had been shown in some studies to have prognostic importance. A study of risk stratification post myocardial infarction reported ejection fraction < 40% by RNVG, ventricular ectopics >10/min and clinical evidence of left ventricular dysfunction as the only independent

predictors of mortality in a multivariate analysis(Multicenter post infarct research group, 1983). Therefore patients with ventricular ectopic activity should be investigated for evidence of left ventricular dysfunction as they may benefit from therapeutic intervention. Vermeulen A (1988) showed ventricular ectopy had no affect on factors influencing return to work post infarct. However there was an association between ventricular ectopic activity and angina.

2.2.2.5 Systolic blood pressure response

An abnormal systolic blood pressure response during exercise testing post myocardial infarction has been shown by several authors to be a predictor of cardiac events and increased mortality (Nielsen JR et al. 1990; Jennings K et al. 1984). Starling MR et al. (1980). reported that a systolic blood pressure rise of ≤ 10 mmHg, a peak systolic blood pressure of ≤ 140 mmHg during exercise testing post myocardial infarction was predictive of future cardiac events Patients with an inadequate rise in systolic blood pressure of ≤ 30 mmHg during exercise testing had a 13% mortality rate in the year following myocardial infarction compared to 2% who had normal blood pressure response (Fioretti P et al. 1984).Inadequate systolic Blood pressure response during exercise implies there is impaired LV systolic function due to myocardial damage at the time of infarct or myocardial ischemia during exercise.

2.2.2.6 Rate Pressure Product

This is defined as the product of heart rate and systolic blood pressure. The absolute rate pressure product and change in rate pressure product can be calculated following exercise testing. Rate pressure product was shown to predicted cardiac death in patients post MI during a mean follow up period of 5.7 years (Saunamaki KI and Anderson JD, 1982).

2.2.2.7 Functional Capacity

The amount of work performed during exercise testing has been found by several authors to be an independent predictor of future cardiac events. Valesco JA (1981) showed that mortality was predicted by exercise duration of < 5 mins in a symptom-limited ergometer

test 3 months post myocardial infarction in 200 patients Weld FM et al. (1997)That showed 38% of patients who exercised for ≤ 6 mins in a low level pre-discharge exercise test died within 1 year compared to 1% of patients exercising for > 6 mins. Jennings K et al. (1984). studied a group of 103 patients who were exercised prior to discharge post myocardial infarction, the mortality rate was 16% at 1 year for patients failing to achieve 5 mets or a heart rate on exercise testing of > 130 beats/min on the Naughton protocol, compared to 2% for patients completing the test. Davidson MD and DeBusk RF (1980) showed that patients failing to achieve a peak workload of ≤ 4 mets during exercise testing 3 weeks post myocardial infarction had a significantly increased rate of subsequent reinfarction, cardiac death and coronary artery bypass surgery during a 2 year follow up period.

Madsen EB et al. (1987). in a study of 466 patients to assess which clinical, demographic and electrocardiographic variables associated with myocardial infarction, predicted functional capacity in predischarge treadmill exercise test, showed that age and resting ST segment shift were the only independent predictors of functional capacity during exercise. Functional capacity analysed as a continuous variable was the most important single predictor of death and reinfarction in this patient group. Patients were categorised on the basis of functional capacity: ≥ 4 mets as low risk, had a 2% mortality rate or reinfarction within 1 year. Patients who failed to achieve this workload were categorised as high risk and had an 18% cardiac event rate at 1 year. A maximum exercise capacity of ≤ 72 watts was shown to predict prognosis (Nielsen JR et al. 1990). Poor exercise tolerance may be related to either ongoing myocardial ischemia or significant left ventricular dysfunction or both. The studies outlined above do not attempt to differentiate between these subgroups as they may have different predictive value in subsequent cardiac event rate. In addition, prognosis of patients with ongoing ischemia could be significantly affected by revascularisation.

2.2.3 Correlation with the extent of coronary artery disease

The relationship between clinical and exercise test variables and the extent of coronary artery disease has been extensively investigated. If a non-invasive assessment can be shown

to correlate with coronary anatomy, then patients who might benefit from revascularisation on symptomatic and prognostic grounds could be identified and referred for confirmatory coronary angiography. In a study of 221 patients exercised 3 weeks post myocardial infarction, coronary angiography was performed on 72 of the 89 patients who had significant ST segment depression during exercise testing(Mannering D et al. 1987). Downsloping or horizontal ST segment depression associated with early onset and late recovery after exercise identified 90% of patients with triple vessel disease. An inadequate systolic blood pressure response of $\leq$ 10% rise from resting values with exercise was also predictive of triple vessel disease.

The relationship between reciprocal changes on the electrocardiogram at the time of acute myocardial infarction, exercise-induced ST segment depression and coronary artery anatomy was studied in 125 patients following myocardial infarction(Murray DP et al. 1997). It was shown that patients with reciprocal changes on the admission ECG had a higher peak cardiac enzyme release and a lower ejection fraction compared to patients with no reciprocal changes. Multivessel disease was significantly more common among patients with reciprocal changes and patients with exercise-induced ST segment depression. ST segment depression during exercise testing compared to reciprocal change had superior sensitivity of 90%, specificity of 61% and a positive predictor of accuracy of 80% in the detection of triple vessel disease.

The extent and distribution of coronary artery disease and left ventricular dysfunction in 123 patients in relation to the presence or absence of ST segment depression during the pre-discharge low level exercise test post myocardial infarction was assessed by coronary angiography at a mean of 50 ± 20 days post myocardial infarction (Griffith LSC et al. 1997). The authors found that patients with ST segment depression of $\geq$ 1 mm had a significantly greater incidence of triple vessel disease, $\geq$ 75% stenosis of the LAD or circumflex artery. Patients with ST segment depression during exercise were shown to have a greater incidence of normal or hypokinetic segmental wall motion abnormalities in areas of the myocardium supplied by significantly stenosed coronary arteries. They concluded

that critical or significant stenosis subtending an area of viable myocardium is required for reversible ischemia during the exercise test, particularly if left anterior descending (LAD) disease is present. Conversely, 88% of patients with no ST segment depression during exercise had akinetic or dyskinetic wall segments. However Peart I et al. (1997) showed that in 100 patients post myocardial infarction under the age of 55 years, only 32% of patients with multivessel disease could be identified by ST segment depression occurring during low level exercise testing at 3 weeks post myocardial infarction. However, at 6 weeks post M.I. a symptom-limited exercise test identified 60% of patients with multivessel disease. Eighty-seven percent of patients with angina pectoris during the symptom-limited exercise test were found to have multivessel disease. This study was restricted to patients of $\leq$ 55 years of age and it is likely that there is a reduced incidence of multivessel disease in this population. Significant stenosis was considered to $\geq$ 50% narrowing of the luminal diameter of a major coronary artery in two orthogonal views. However, no attempt was made to correlate the exercise findings with the severity of stenosis of individual arteries.

A normal exercise test response post myocardial infarction identified approximately 75% of patients with either no coronary artery disease or single vessel disease in 40 survivors of uncomplicated myocardial infarction (Fuller CM et al. 1981). This emphasises the value of a negative test result which can be used to identify patients with a good prognosis who could potentially be discharged early from clinical follow up. The prognostic value of coronary angiography was compared to exercise testing and left ventriculography in a study by De Feyter PJ et al. (1982).of 179 patients. Increased morality was associated with ejection fraction < 30% 3 vessel disease and reduced exercise capacity (<10 ins Bruce Protocol). Exercise to this level would not normally be considered as reduced functional capacity. Failure to achieve the mean or median exercise time would perhaps been a better definition of reduced workload.

2.2.4 The effect of vessel patency on outcome

The prognostic importance of infarct vessel patency following coronary angiography at a mean of 12 days post infarct, on clinical outcome in 97 patients with single vessel disease

was studied by Wilson WW et al. (1988). A patent vessel was associated with non q wave infarct, increased ejection fraction and lack of collateral circulation There was no difference in cardiac event rate (cardiac death, further myocardial infarction, unstable angina, CABG or PTCA) in patients with or without patent vessels. Thrombolysis was not given in this study which was reflected in the patency rate of 41% at angiography. Patency was assessed a 12 days post infarct an therefore did not necessarily reflect salvage of myocardium associated with early patency. Reversible defects on thallium ^{201} scintigraphy were however associated with vessel patency. ST segment depression during predischarge exercise testing did not predict vessel patency or clinical outcome.

A decision scheme for coronary angiography in post infarct patients was developed in patients under 75 yrs (Ross et al. 1989). Patients with resting reversible ischemia beyond day 5 post myocardial infarction, history of previous MI, evidence of peri infarct LVF exercise induced ischemia and reduced exercise capacity should undergo coronary angiography as intervention may reduce the average mortality rate in this group estimated to be around 16%.

2.2.5 Type of Myocardial Infarction (Q wave v Non Q wave)

In a prospective study of 241 patients ≤ 65 years of age with uncomplicated acute myocardial infarction, showed that in patients with non-Q wave infarction there was a reduction in infarct size, improvement in left ventricular function but no difference in overall mortality compared to Q wave infarcts (Gibson RS et al. 1987). In patients with non-Q wave infarcts, 54% had patent coronary arteries in the infarct territory with coronary angiography at a mean of 11 days post infarct. In addition in patients with non-Q wave infarct, there was an earlier peak in creatine kinase release and an increased incidence of reversible thallium defects in the infarct zone. Patients with non-Q wave infarcts had a significant increase in re-infarction rate compared to Q wave infarcts (18% v 6%) during 30 months of follow up. There was a higher incidence of revascularisation by means of CABG and PTCA performed in the non-Q wave infarct group (33% versus 19%). Risk statification of 141 patients with first non q wave infarct was performed using clinical and exercise

variables. Failure to perform the exercise test was associated with adverse outcome. Patients with ST segment depression had an increased incidence of cardiac events in the first year post infarct with an odds ratio of 3. However the discriminatory value of reversible ischemia was limited to a sub group of patients with pulmonary congestion (Krone DJ et al. 1989). Miranda CP et al. (1991).showed that in both Q wave and non Q wave infarctions ST segment depression ≥ 1 mm was a marker of the severity of coronary artery disease They found in a 4.4 year follow up period patients with Q wave and non Q wave infarcts had a similar survival rate (81% after non-Q wave, 85% after Q wave). However, they found a significant difference between the infarct-free survival rates of patients with (72%) and without (86%) severe coronary artery disease. However, the authors did not consider time scale of cardiac events to determine whether the events occurring in non-Q wave infarction occurred early following infarction. The mean ejection fraction in the group with Q wave myocardial infarction was 51±13% versus 68±11% in the group with non-Q wave infarction. Therefore, the preservation of left ventricular function with non-Q wave infarct did not appear to confer improved survival. However, the mean ejection fraction for both groups would still be considered within normal limits and a sub group analysis of patients with abnormal left ventricular function ≤ 40% ejection fraction (Q wave versus non-infarct) may have altered long-term survival. 29% of patients underwent revascularisation by means of PTCA or CABG. These patients were assessed for recurrent infarcts to the point of intervention and were thereafter censored from further survival analysis. The positive predictive accuracy of the exercise test in both non-Q wave and Q wave myocardial infarction to identify severe coronary artery disease was improved by using the criteria of ≥ 2 mm ST segment depression to define reversible ischemia. These studies suggest that non-Q wave infarction and Q wave infarction do not represent the same anatomical or clinical entity and should not be combined in studies of myocardial infarction.

2.2.6 Exercise Testing with Nuclear Medicine

Multiple thallium defects were shown to identify 94% of patients at high risk of recurrent cardiac event during the first year of follow up, compared with 56% with other abnormal exercise test results (Gibson RS and Taylor GJ, 1981). The same author showed that low level exercise testing with thallium scintigraphy could identify 71% of post M.I. patients with multiple coronary artery disease (Gibson RS et al. 1983).

Thallium imaging defects in the non-infarct territory, inadequate blood pressure response to exercise, inadequate heart rate response or ST segment depression at a low workload were highly predictive of left main or three vessel disease in a group of 40 patients who had previously sustained myocardial infarction and who had been referred for cardiac catheterisation (Patterson RE et al. 1997). Thallium 201 scintigraphy performed by experienced staff in conjunction with early exercise testing post myocardial infarction has increased sensitivity and specificity for the detection of myocardial ischemia (Detrano et al. 1997). Thallium 201 scintigraphy accurately detected previous myocardial infarction and was more accurate than clinical or electrocardiographic responses to exercise for detection of coronary artery disease in non-infarct territory in a group of 66 men with previous myocardial infarction (Chouraqui P et al. 1990). Gibson RS and Watson DD in 1991 concluded that the advantages of thallium 201 scintigraphy were:

1. Increased sensitivity detecting myocardial ischemia.
2. The ability to localise ischemia to a area supplied by a specific coronary artery.
3. The ability to identify exercise-induced left ventricular dysfunction.
4. Improved risk stratification of individual patients

Ninety-seven patients with uncomplicated q wave or non q wave myocardial infarction due to single vessel disease not receiving thrombolysis or PTCA were studied (Wilson WW et al. 1988). The relationship between myocardial ischemia assessed by the pre-discharge exercise thallium 201 scintigraphy, and vessel patency defined by coronary angiography at a mean of 12 days post infarct, was studied. A significant stenosis was considered as ≥50%

luminal narrowing. Patients were followed for a mean period of 39 months. However, there were no deaths indicating excellent prognosis in this group. 6% had a further myocardial infarction and 26% were hospitalised with unstable angina. Exercise-induced angina and ST segment depression during exercise were not predictive of recurrent cardiac events. However, in a quantitative assessment thallium 201 redistribution was greater in patients who experienced a late ischemic event. The infarct-related artery was angiographically patent in 41% of patients. Patency did not influence event-free survival, although in the absence of thrombolytic therapy, this represents spontaneous reperfusion which could occur at any point post-infarct, and does not equate with accelerated patency and resultant myocardial salvage thrombolysis. Vessel patency, reversible infarct zone thallium defects and a higher ejection fraction were associated with the non-Q wave infarction.

A study of viability of myocardium post infarct showed 40% of fixed defects with thallium 201 scintigraphy had evidence of metabolic activity with positron emission tomography, using nitrogen-13 ammonia and fluorene-182 fluoro-deoxyglucose (FGD) (Tamaki N et al. 1988). The authors suggests that such patients may benefit from revascularisation. Persistent defects without metabolic activity had impaired wall motion.. However, the study did not perform coronary angiography to define the status of the infarct related vessel at the time of PET scanning. Following thrombolysis for acute myocardial infarction Thallium 201 scintigraphy identified more patients with reversible ischemia than symptom limited treadmill exercise testing (Jain A et al. 1997)

Early submaximal thallium 201 SPECT exercise testing following thrombolysis for acute myocardial infarction was evaluated by Stewart RE et al (1991).The extent of Thallium 201 defect correlated with LV function. Detection of coronary disease in the non infarct territories by thallium 201 SPECT was poor. The size of perfusion defect was associated with occlusion of the infarct related artery on repeat angiography .

2.2.7 Stress Testing with Echocardiography

Risk stratification was reviewed by Crawford MH (1997) after myocardial infarction with exercise and doppler echocardiography. It is possible to image 80-95% of patients before and after treadmill testing. New or worsening wall motion abnormalities identify 63-80% of patients at risk of recurrent cardiac events. In addition, exercise echocardiography detected multivessel disease with a sensitivity of 80% and a specificity of 90%. However, this technique must be very operator-dependent as echocardiographic images must be obtained very rapidly after the termination of exercise.

2.2.8 Pharmacological Stress Testing

Severi S and Michelassi C (1997) reviewed preliminary data on intravenous dipyridamole echocardiography, suggesting its usefulness for diagnosis and risk stratification in patients with coronary artery disease and provides additional information to that provided by exercise electrocardiography Dipyridamole echocardiography with stress testing performed early after acute myocardial infarction in a group of 131 patients prior to hospital discharge was safe, feasible and could accurately predict the extent of coronary artery disease and the clinical outcome up to 18 months (Bolognese L et al. 1991). Coma-Canella I, (1991). reported that if ST segment depression occurred during dobutamine stress testing in a study of 104 patients post myocardial infarction their prognosis was significantly worse the test. The safety and usefulness of dipyridamole 201 thallium scintigraphy in the prediction of further cardiac events after acute myocardial infarction was evaluated in 51 patients (Leppo JA et al. 1984). It was concluded that dipyridamole thallium scan was superior to routine submaximal exercise test in the prediction of subsequent cardiac events.

The usefulness of dipyridamole thallium 201 imaging compared to submaximal exercise thallium testing for risk stratification following thrombolysis was studied by Lette J et al. (1990). A case study described a patient who was shown to have severe perfusion defect on dipyridamole thallium imaging, but only a small ischemic area on the submaximal exercise test and this correlated with severe disease of the left anterior descending and suggested that

dipyridamole thallium imaging was of additional benefit in non-invasive assessment of certain patients.

2.2.9 The Effect of Therapy

There is controversy over the usefulness of exercise testing post myocardial infarction in patients taking betablocking agents. In 207 patients post myocardial infarction it was found that betablocking agents did not influence the ability of a low level exercise test to identify patients at high and low risk of further cardiac events (Krone RJ et al. 1987). Patients on betablocker obviously had a lower resting heart rate, peak exercise heart rate and rate pressure product. Murray DP et al. (1988) confirmed these results in a group of 125 patients who underwent cardiac catheterisation Betablockade did not influence the ability of the test to identify patients at high risk of subsequent cardiac event. However, it did reduce the sensitivity of the test in identifying patients with multivessel disease. Mannering D et al. (1987). showed that there was no significant difference in the prevalence of ST segment depression and abnormal systolic blood pressure response in patients on betablockers, and demonstrated that betablockers did not affect the accurate detection of triple vessel disease post infarct However, Curtis JL et al. (1991). Showed that betablockers administered following myocardial infarction significantly reduced the prevalence of ST segment depression during a submaximal exercise test and can therefore alter risk stratification.

If patients have reversible ischemia, it would be expected from clinical trials of anti-anginal agents that there would be a delay to time of onset of ST segment depression when patients were taking these drugs. However, it is likely that patients would still display reversible ischemia if exercised maximally. Therefore, during low level exercise testing a reduced incidence of ST segment depression would be expected.

3. EXERCISE TESTING FOLLOWING THROMBOLYSIS FOR ACUTE MYOCARDIAL INFARCTION

3.1 Predictive value of exercise testing post thrombolysis

GISSI I was the first large scale trial to demonstrate the benefits of thrombolysis. In a study of 11,806 patients there was a significant reduction in 21 day mortality following streptokinase (10.7%) versus placebo (13%)(The GISSI Working Group 1986). There was a 10% reduction in mortality at 12 months. This led to the widespread use of intravenous thrombolytic therapy in myocardial infarction. Thrombolysis results in salvage of myocardium by reperfusion of the infarct-related artery but in 70% of cases there is a residual stenosis. This may result in an increased incidence of recurrence ischemic events, including reversible ischemia during the exercise test. Given that thrombolysis has resulted in a different coronary anatomy post infarct compared to previous treatment strategies, the predictive value of exercise testing post-infarct requires re-evaluation in the thrombolytic area.

3.1.1 Recurrent Early Ischemia

Schaer DH et al. (1987) compared the incidence of recurrent early ischemic events after intracoronary administration of streptokinase for acute myocardial infarction Patients of < 70 yrs of age admitted within 4 hrs of the onset of symptoms of acute myocardial infarction who had diagnostic electrocardiographic changes were studied. A pre-treatment angiogram was performed in 81 patients. Those patients (n=64) with a total occlusion of the infarct-related artery were randomised to receive intracoronary streptokinase or intracoronary nitrates. 17 patients with a subtotal occlusion did not receive thrombolysis or control therapy. Recurrent ischemic events were defined as:

1. Spontaneous angina at rest or during ward ambulation
2. Angina provoked during pre-discharge exercise test
3. Reinfarction

Of the 35 patients who received streptokinase, 21 (60%) reperfused within 90 mins. Of the 29 patients who were randomised to receive intravenous nitrates only 3 reperfused at 90 mins. 65% of those patients who had a subtotal occlusion and 48% of those patients who reperfused had an ischemic event. However, only 11% of patients who failed to reperfuse had a further ischemic event compared to the patients in the subtotal occlusion or reperfusion group ($p < 0.01$). Patients with single vessel disease were also analysed separately to eliminate the effect of multivessel disease as a cause of ischemic events. Although the numbers in this subgroup were small, those patients with a subtotal occlusion or those patients who reperfused at 90 mins following thrombolysis had an increased incidence of ischemic events. The results of the exercise testing were not analysed separately from the other ischemic events. The study did not include non q wave infarction. It is therefore interesting that 17 patients had subtotal occlusions at the time of pretreatment angiography. The authors therefore concluded that patent infarct-related arteries had a higher prevalence of in-hospital ischemic events relative to patients without reperfusion.

Topol EJ et al. (1987) evaluated exercise testing 3 days after uncomplicated acute myocardial infarction in 53 consecutive patients who had received reperfusion therapy by means of thrombolysis $\pm$ coronary angioplasty. A heart-rate limited (140 beats/min) treadmill exercise test accompanied by thallium 201 scintigraphy was used. 26% of patients were shown to have a reversible perfusion defect. Of the 14 patients with a perfusion defect, 4 had an adverse clinical outcome in the first 10 days post myocardial infarction. 69% of patients had no evidence of reversible ischemia and none of these patients experienced recurrent ischemic events during hospital admission. The study however does not state whether the patients were randomised to receive thrombolysis alone, angioplasty alone or thrombolysis plus angioplasty. It also fails to state the criteria for acute angioplasty. The authors could not find a clear relationship between residual stenosis of the infarct-related artery and reversible ischemia during the exercise test. They did not study the influence of multivessel disease. Non q wave infarcts were included in this study but no subgroup analysis was performed.

3.1.2 Thallium Scintigraphy

A study of 236 patients with thallium 201 exercise scintigraphy 9 to 14 weeks after acute myocardial infarction was performed by Van Der Wall EE et al. (1997). 128 patients had received intracoronary streptokinase and 108 patients control therapy. 13 patients who received thrombolysis reinfarcted prior to thallium scintigraphy. Revascularisation was performed on the basis of clinical symptoms of angina and were evenly distributed between thrombolytic and control groups between patients allocated to the thrombolytic group. There were no significant differences in symptoms, electrocardiographic changes, haemodynamic performance or peak workload during exercise testing. There was a significant increase in the number of segments with normal thallium activity in the thrombolytic group, indicating myocardial salvage and improved perfusion. No attempt was made to relate patency, thallium redistribution and ST segment changes during exercise within the thrombolytic group, and no assessment was made of residual stenosis of the infarct-related artery or additional vessel disease. The authors however concluded that in patients with first anterior myocardial infarction, early thrombolysis followed by additional revascularisation procedures leads to an improved myocardial perfusion, without an increased occurrence of exercise-induced ischemia.

The functional significance of predischarge exercise thallium 201 testing following intravenous streptokinase for acute myocardial infarction in 21 patients was studied by Touchstone DA et al. (1988). They concluded that both delayed and reverse redistribution during predischarge exercise thallium 201 imaging are associated with myocardial salvage, as defined by serial improvement in regional systolic function. However, despite the high patency rate of the infarct-related vessel (76%) only 30% demonstrated an improvement in regional function associated with delayed or reverse redistribution on the predischarge exercise test.

171 patients recovering from acute myocardial infarction were followed for a mean of 374 days by Tilkemeier PL et al. (1990) to determine whether the use of thrombolytic therapy in acute myocardial infarction affected predictive value of low level exercise thallium 201

testing. Sixty-four of the 171 patients (37%) received thrombolysis. There was no significant difference in the incidence of death, reinfarction, coronary artery bypass surgery or PTCA in patients treated with thrombolytic therapy versus those without interventional therapy. Only in the non-intervention group was the presence of ST segment depression of $\geq$ 1 mm a predictor of cardiac events with a sensitivity of 81%. This implies that ST segment depression during exercise testing post myocardial infarction in patients who have received thrombolysis no longer has the same predictive value. In those patients who received thrombolysis, left ventricular dilatation was the only predictor of future cardiac events with a modest sensitivity of 55%. Exercise test performed was submaximal and may not reflect the true incidence of reversible ischemia. Routine cardiac catheterisation was not part of this study and no conclusions regarding patency in those patients with thrombolysis can be made or relationship with recurrent ischemic events defined. Therapeutic decisions were made on the basis of the exercise test thallium study.

Hamouratidis N et al. (1991) in a placebo-controlled study, assessed the value of exercise testing in patients with acute myocardial infarction treated with intravenous streptokinase The authors attempted to relate the results of exercise testing to recanalisation of the infarct-related artery by performing angiography at a mean of 22.9$\pm$7 days. 31 patients who received intravenous streptokinase and 39 patients who received placebo were exercised to a workload of 6 mets by the modified Bruce protocol, 3 weeks following myocardial infarction. There was no significant difference in the number of positive exercise tests as defined by typical angina, or ST segment depression of $\geq$ 1 mm, or both in the streptokinase or placebo group. However, the patients treated with streptokinase had a significant increase in the rate of recanalisation (65% versus 38%). Patients with multivessel disease had an increased incidence of abnormal exercise responses. In patients with recanalised arteries there was an increased incidence of negative exercise tests. However, in these patients there was no attempt to assess the viability of the myocardium supplied by the infarct-related artery. In patients with an occluded artery there was an increased incidence of collateralisation. The authors also used the combined criteria outlined above to define a positive exercise test and did not consider the development of angina or ST segment

depression as separate entities. They also did not investigate other abnormal exercise responses such as inadequate rise in systolic blood pressure or development of ventricular ectopic activity. Coronary angiography was performed late at 22.9 days and it is likely that time-dependent reperfusion has occurred without salvage of the myocardium in a number of patients.

3.1.3 Clinical and Exercise Variables

The effect of thrombolytic therapy on the chronotropic response to exercise in patients recovering from AMI was studied by Svendsen JH et al. (1992). 41 patients received intravenous streptokinase and 44 patients placebo within 12 hrs of the onset of symptoms of myocardial infarction. symptom-limited bicycle ergometry was used 12 days post myocardial infarction to assess a variety of exercise test responses in both groups. Patients treated with streptokinase had a significantly greater maximum heart rate and rate pressure product at peak exercise ($p < 0.01$). The total exercise time, occurrence of angina, time to onset of angina, maximum ST-T changes, and left ventricular ejection fraction were not different in the two groups. In this study, patients were included up to 12 hrs following the onset of symptoms of acute myocardial infarction and therefore the benefits of thrombolysis may not be apparent in those treated between 6 and 12 hrs and may reduce the clinical distinction between treated and placebo groups. Coronary angiography was not performed to determine the outcome of treatment in terms of patency of the infarct-related vessel.

Data from GISSI-2 (GISSI Working group, 1990, 1993, 1993) considered the clinical and exercise variables which predicted non fatal reinfarction and 6-month mortality post-myocardial infarction following thrombolysis in 10,219 patients. Inability to perform exercise test, early or late left ventricular failure, echocardiographic left ventricular dysfunction, advanced age, complex ventricular arrhythmias and previous myocardial infarction were all independently predictive of mortality. Early post-infarct angina, a positive exercise test (angina or ST segment depression 80 m.secs after the J point) or anterior myocardial infarction did not predict clinical outcome in terms of mortality at 6 months. Definition of a positive exercise test did not include low workload or abnormal

haemodynamic response. No angiographic assessment was made. Overall mortality was 3.5% at 6 months. Rates of CABG and PTCA were low (7%)but mortality analysis included these patients and this intervention may have influenced the clinical outcome of these patients. In patients with late left ventricular dysfunction, 60% did not exhibit echocardiographic evidence of LV dysfunction in the peri-infarct period. In the prediction of outcome, the study did not analyse ST segment depression alone but included angina in the definition of a positive exercise test. The test was therefore qualitative. The majority of patients were on beta-blockers which may reduce the ischemic response during exercise. There appears to be a reduced incidence of ventricular dysrhythmias post-thrombolysis and this may be related to reduction in scar tissue formation reperfusion therapy. Increasing age is associated with multi-vessel disease and changes in cardiovascular function, and although the elderly cohort in this study is limited to $\leq$ 75 yrs, increasing age is still an independent predictor of outcome.

The ability of the treadmill test post-infarct in 256 patients treated with thrombolysis was reassessed in 1993; two hundred patients underwent late coronary angiography as part of the study by Stevenson R et al. (1993). Intervention was offered on the basis of the angiogram result (ie prognostic grounds) and symptoms of limiting angina.

Cardiac events: Cardiac death, myocardial infarction, unstable angina, coronary artery bypass surgery and coronary angioplasty were noted over a follow-up period of 12 months post-infarct. A symptom limited modified Bruce exercise test was performed. Event free survival showed ST segment depression at a low workload and failure to achieve a median workload was predictive of future cardiac events. The ST depression alone, ST elevation, inadequate haemodynamic response, ventricular extrasystoles did not predict future events. Sudden death only occurred in 5 patients and no attempt was made, due to the small numbers, to analyse mortality data separately. The predictive value of the exercise test of cardiac events is shown below in table 3.1

	Sensitivity	Specificity	Positive Predictive Accuracy	Negative Predictive Accuracy
ST↓	68	53	20	88
ST↓ low workload	50	73	26	89
Workload < 7 mets	70	49	21	89
Abnormal Test	83	25	17	89

Table 3.1 The predictive value of the exercise test (modified from Stevenson et al)

Thus, the test has modest sensitivity and specificity but low positive predictive accuracy. However, the high negative predictive accuracy indicates that a negative test result defines a low risk population who may not require intensive cardiac follow-up. The entry criteria for this study included non q wave infarcts and did not sub classify types of myocardial infarction in the analysis. Hence, non q wave infarction associated with early recurrent ischemic events may have affected the results. No attempt was made to correlate infarct related vessel patency or additional vessel disease with outcome. Revascularisation was performed on patients for prognostic reasons as well as symptomatic. Although it may not be valid to include these patients in the analysis, removing them from the data did not affect the overall result.

The value of coronary angiography following thrombolysis for acute myocardial infarction was assessed in 1,043 patients in prediction of mortality in the European Cooperative Study Group where patients were randomised to alteplase/placebo or alteplase/or PTCA (Arnold AER et al. 1993). The age limit was ≤ 71 years and patients had ≥ 30 minutes of chest pain with ST segment elevation. A symptom limited sub-maximal exercise test was performed. Additional exercise end points were significant arrhythmia, systolic blood pressure fall of ≥ 15 mmHg, and achievement of maximum heart rate (200 - age).Radionucleotide ventriculogram was performed prior to the exercise test and full ECGs were scored by Silvester scoring system and cardiac infarction injury score. Clinical variables considered were age, sex, sum of ST elevation, time to treatment, medical therapy, angiography and

infarct size by cardiac enzyme. Exercise test variables included ST segment depression, ST elevation, maximum workload and inability to perform exercise. Global left ventricular ejection fraction from RNVG and contrast left ventriculography and severity of coronary artery disease from angiography performed at 10-22 days were also considered. Predictors of mortality included age, infarct size on enzymes, clinical signs of heart failure ,RNVG ejection fraction, inadequate systolic blood pressure rise and extent of coronary artery disease independent of treatment in a multivariate analysis. Symptoms of angina at rest or during exercise did not predict mortality. Inadequate systolic blood pressure rise led to a 2.2-fold increase in mortality. ST segment elevation or depression did not contribute to risk assessment. Multi-vessel disease, residual stenosis and patency of infarct related artery were related to mortality. Left main disease with a residual stenosis of $\geq$ 50% had a low incidence (0.9%)and did not predict mortality but this may be subject to a Type II error. In this study, revascularisation was performed if clinically indicated, and these patients were not censored from mortality analysis and therefore this may affect the overall result, assuming revascularisation influences mortality. Coronary angiography was performed late at 10-22 days and no early assessment of patency or residual stenosis was made. It is conceivable that early patency may have more influence on clinical outcome.

The thallium 201 exercise test after thrombolysis for acute myocardial infarction was shown to have limited prognostic value in 210 patients followed for a mean of 21 months (Miller TD et al. 1995). No single exercise variable predicted outcome and the only variable predictive of outcome was left ventricular dilatation. The study did not state whether non q wave infarcts were included. Coronary angiography was performed within 3 months of the thallium study and therefore there was no early assessment of the effects of thrombolysis. The exercise test was sub-maximal. There is a relationship between the severity of coronary artery disease and overall mortality ($p = 0.03$), but not with cardiac death or non-fatal re-infarction. They applied very strict criteria for cardiac death. However, it is likely that overall mortality does on the whole reflect cardiac death and that a percentage of the deaths defined as non cardiac would be misclassified due to lack of information regarding the terminal event.. The trial was not randomised and the number of events were very low

and this may have produced a Type II error. Referral for early revascularisation may improve survival and therefore may bias the mortality results.

The prognostic value of a normal submaximal predischarge exercise test following thrombolysis was assessed in 80 patients treated conservatively following myocardial infarction (Marx et al. 1997). 4 patients required revascularisation on clinical grounds and 23 had ischemic events over a mean follow up period of 12 months. This study contains relatively small numbers and does not define the criteria for a submaximal test, but it suggests limited value of exercise testing post infarct following thrombolysis. Administration of thrombolysis late between 12 and 49 hours was shown to reduce the incidence of exercise induced Ischemia compared to a control

3.1.4 Reciprocal Depression during Exercise testing following thrombolysis.

ST depression occurring during exercise in conjunction with ST segment elevation (Reciprocal Depression) in the site of infarct, as defined by sequential changes in the ECG may simply be an electrical phenomenon and not indicative of a residual stenosis of the infarct related artery or additional vessel disease (Stevenson RN et al. 1994)

Isolated but not Reciprocal ST depression predicted multivessel disease (predictive positive accuracy of 72%)Absence of ST depression was predictive of patency of the infarct related artery at angiography at a mean of 30 days post infarct. Reciprocal or isolated ST depression did not identify site of infarct. Isolated ST segment depression occurred more frequently in non Q wave infarcts and in association with angina during exercise. There was a trend for reciprocal ST segment depression to be related to occlusion of the infarct related vessel, reflecting unsuccessful thrombolysis and more extensive myocardial necrosis. Angiography was performed late in this study and no attempt was made to assess viability of the myocardium subtended by the infarct related vessel, therefore the relevance of patency in this context is questionable. However this study suggests that reciprocal depression should be considered as a negative result in risk stratification post infarct.

3.2 Coronary Anatomy Post Thrombolysis and Recurrent Ischemia

Sutton JM and Topol EJ (1991) assessed the significance of negative exercise thallium 201 exercise tests in the presence of a critical residual stenosis after thrombolytic therapy for acute myocardial infarction. The authors state that despite the overall benefits of thrombolysis, there is a limited 50-75% reperfusion rate at 90 mins , 5-15% reocclusion rate and a 70% incidence of a significant residual stenosis ($\geq$ 70%) in the infarct-related vessel. 101 patients who had a significant residual stenosis following thrombolysis $\pm$ PTCA at angiography at 90 mins post treatment were exercised by a submaximal exercise treadmill test accompanied by 201 scintigraphy on the third or fourth hospital day post infarct. Exercise tests were terminated at a target heart rate of 140 beats/min in the absence of clinical or electrocardiographic evidence of reversible ischemia. The electrocardiographic diagnosis of reversible ischemia required $\geq$ 2 mm of downsloping or horizontal ST segment depression. Thallium studies revealing fixed perfusion defects only, were considered as negative, as were tests which had a fixed perfusion defect with only small areas of peri-infarct redistribution in the absence of clinical or electrocardiographic myocardial ischemia. A positive test was considered as:

1. Significant completely or partially redistributing thallium 201 defect in any myocardial region
2. A predominantly fixed thallium 201 defect with peri-infarct redistribution associated with abnormal exercise electrocardiographic changes

Table 3.2 shows the clinical data relating to exercise test outcome in all patients with a $\geq$70% residual stenosis. As shown, the only significant difference was in the clinical data for patients with and without reversible ischemia is an increased peak CK level in those with no reversible ischemia during exercise testing. Table 3.3 shows demographic, clinical and exercise thallium variables for patients with and without reversible ischemia during exercise testing treated with thrombolysis alone. Reversible ischemia was more common in patients with anterior myocardial infarction ($p < 0.03$) and again, size of infarct defined by peak CK level was higher in those with no reversible ischemia during exercise. Therefore

the effects of PTCA did not significantly influence stress test outcome. The effects of multivessel disease stress outcome were eliminated by considering patients with single vessel disease as an isolated subgroup. Results are shown in Table 3.4.

Peak CK levels again were higher in patients with no reversible ischemia, but there was no other difference between the groups in terms of clinical or exercise test variables. The authors concluded a negative early stress thallium 201 tomogram after successful reperfusion therapy was associated with more extensive myocardial necrosis and not delay in therapy or inadequate exercise performance. Angina during exercise was associated with a three-fold increase in the detection of significant reversible ischemia by thallium 201 scintigraphy.

	Positive ETT	Negative ETT
Patients (n)	52	49
Age (yr)	58 ± 10.4	54 ± 10.0
Male sex (n)	48(92)	39(80)
Time to t-PA therapy (min)	199±89	186±132
Prior myocardial infarction (n)	8(15)	5(10)
Infarct location		
Anterior/lateral(n)	29(56)	23(47)
Inferior/posterior	23(44)	26(53)
Infarct artery (n)		
LAD	29(56)	23(47)
RCA	18(35)	21(43)
LCx	5(10)	3(6)
Bypass Graft	0	2(4)
Peak CK level (IU/ml)	2605±1805	3820±3123*
Multivessel disease (n)	21(40)	19(39)
LVEF by ventriculography (%)	54±15	53±14
Residual stenosis of infarct vessel(%)	90±9	88±9
Heart failure (Killip's class II or III) (n)	33(63)	28(57)
PTCA performed (n)	29(56)	30(62)
Post-PTCA residual stenosis (%)	61±33	55±29
Exercise Test		
Peak heart rate (beats/min)	123±18	129±19
Peak systolic pressure (mmHg)	154±33	150±34
Time stressed (min)	6±3	8±12

Table 3.2 Clinical Data For All Patients With > 70% Residual Stenosis (modified from Sutton JM and Topol EJ 1991)

Values are mean±SD where appropriate; Values in parentheses are percentage, *p=0.04

	Positive ETT	Negative ETT	P value
Age (yr)	57±10	51±10	0.06
Male sex (n)	21(91)	17(89)	0.40
Infarct location (n)			
Anterior/lateral	16(70)	7(37)	0.03*
Inferior/posterior	7(30)	12(63)	0.03*
Multivessel disease (n)	6(26)	5(26)	0.98
Time to t-PA therapy (min)	175±85	202±173	0.50
Peak CK level (IU/ml)	2399±1443	3290±2504	0.04*
LVEF by ventriculography	56±14	(%)55±13	0.64
Heart failure (Killip's class II or III) (n)	12(52)	9(47)	0.76
Post thromboltyic stenosis (%)	85±15	82±17	0.20
Exercise thallium study			
Exercise-induced angina (n)	6(26)	1(5)	0.07
Peak heart rate (beats/min)	123±21	172±17	0.40
Peak systolic pressure (mmHg)	156±37	157±30	0.92
Time stressed (min)	6±2	6±2	0.60

Table 3.3 Stress Test Outcome For Patients Treated With Thrombolysis Alone (modified from Sutton JM and Topol EJ 1991)

Values are mean±SD where appropriate; Values in parentheses are percentage;

	Positive ETT(N=31)	Negative ETT(n=30)	P value
Age (yr)	57±10	54±11	0.31
Male sex (n)	27(87)	23(77)	0.30
Prior MI (n)	3(10)	1(3)	0.32
Infarct artery (n)			
LAD	20(65)	16(53)	0.66
RCA	10(32)	13(43)	0.66
LCx	1(3)	1(3)	0.66
Time to t-PA therapy (min)	183±94	180±142	0.93
Peak CK level (IU/ml)	2396±1891	3936±3282	0.03
LVEF by ventriculography(%)	57±14	52±13	0.18
Heart failure (Killip's class II or III) (n)	15(48)	16(13)	0.89
Post-thrombolytic stenosis(%)	87±15	(%)88±11	0.75
PTCA performed (n)	13(42)	16(53)	0.37
Exercise thallium study			
Exercise-induced angina (n)		2(7)	0.07
Peak heart rate (beats/min)	121±19	131±17	0.05*
Peak systolic pressure(mmHg)	153±35	152±31	0.95
Time stressed (min)	6±3	6±2	0.48

Table 3.4 Stress Test Outcome For Patients With Single-Vessel Disease Only
(modified from Sutton JM and Topol EJ 1991)

Values are mean±SD where appropriate, Values in parentheses are percentage;

The lack of provokable residual ischemia after thrombolysis in patients with a significant stenosis of the infarct-related vessel was also seen in phase IIB of the TIMI study (The TIMI Study Group, 1989,1993). The results of exercise testing in the TIMI II trial did not predict reinfarction. It is possible that infarct-vessel remodelling following acute angiography occurs in the first few days following thrombolysis, therefore early angiography does not reflect the situation prior to exercise testing. The authors noted a 10-15% rate of conversion in a positive test and full symptom-limited thallium 201 stress testing at 6 weeks post infarct. The use of delayed (24 hour rest scanning) may have improved detection of viable myocardial ischemia.

In the thrombolysis in myocardial infarction (TIMI) II Trial, 2,502 patients were exercised by supine ergometry within 2 weeks of myocardial infarction. Patients with ECG changes of ST elevation or a typical history were randomised to a conservative or invasive management. Patients in the invasive group all underwent coronary angiography at 18 to 48 hours post infarct. If the infarct-related vessel had a significant residual stenosis, patients received PTCA. In the conservative group, patients were investigated invasively if they experienced post-infarct unstable angina or exercise-induced reversible ischemia (ST segment depression $\geq$ 2mm), a reduction in systolic blood pressure ($\geq$ 20 mmHg), reduced exercise ejection fraction or complex ventricular arrhythmias. The test results was considered inconclusive if patients could not achieve a heart rate of 120 beats/minute or a workload of 400 Kpm.

Cardiac Events: Reinfarction, congestive cardiac failure, angina pectoris, CABG or further PTCA and death were recorded for a period of one year post-infarct. There was no significant difference in early cardiac event rate, incidence of ST depression during exercise, or the numbers able to perform exercise between the conservative and invasive groups. Elderly subjects, women, presence of multi-vessel disease, patients with previous myocardial infarction, were significantly less likely to manage the exercise test. Patients unable to exercise had a significant increased incidence of all cardiac events and specifically mortality at one year. There was no difference in rest or ejection fractions

between invasive and conservative groups. There was also no difference in the incidence of ST segment depression between the groups. Exercise test variables; ST depression, ST elevation, angina, peak heart rates and systolic blood pressure response did not predict the clinical outcome in either group or both groups combined. ST segment elevation during exercise was associated with reduced ejection fraction ($p < 0.001$) and was associated with an increase in one year mortality. Therefore, ST elevation may be associated with reduced left ventricular function which is known to be associated with poor outcome. Those patients who had undergone PTCA and had ST segment depression during exercise had an increased incidence of multi-vessel disease and a higher mean per cent residual stenosis of the infarct related artery ($p > 0.001$). There was an overall trend of increased per cent residual stenosis in patients with ST segment depression when both groups were combined. The presence of collateral circulation and TIMI grade of reperfusion with the infarct related artery did not relate to ST segment depression during exercise. Table 3.6 below, modified from TIMI II data shows the relationship between exercise induced ST segment depression in both groups and the findings of cardiac catheterisation. Although the ST segment depression ≥ 1 mm was considered as an abnormal exercise response, indication for angiography was set at ≥ 2 mm ST segment depression. Therefore less patients in the conservative group underwent angiography and thus may have influenced the results. TIMI patency grade was assessed before PTCA in the invasive group at 18-24 hours post-infarct. This implies the patients were assessed at a variable time point post-infarct and includes no early assessment of patency at 90 minutes post-thrombolysis. Early patency is likely to be the main determinant of myocardial salvage and may be more closely related to exercise induced myocardial ischemia. Low workload without additional reversible ischemia was treated as an inconclusive exercise test result and not an indication for angiography. Other studies have shown low workload to be related to poor left ventricular function and, therefore, should have been considered along with inadequate systolic blood pressure response and ejection fraction during exercise as an indication for angiography. Few patients had exercise induced ventricular arrhythmias or isolated premature ventricular beats and this is not associated with increased risk. Patients with the LAD artery as the infarct related vessel were less likely to develop ST segment depression. Before the widespread use of

thrombolytic therapy, 30% of patients post-infarct had ST segment depression and 20% angina during the exercise test. Post-thrombolysis ± PTCA the incidence of ST segment depression during exercise testing has fallen to around 12% and angina to 5%. This refutes the concept that there is an increased incidence of ischemic events post-thrombolysis, but may reflect the addition of PTCA and early revascularisation in the TIMI 11 study. Patients also received thrombolytic therapy very early at ≤ 4 hours post-onset of symptoms. If the patients had residual stenosis of ≤ 60% with one vessel disease following PTCA they were classified as 0 vessel disease during follow-up. An insignificant coronary stenosis may not result in reversible ischaemia during Exercise Testing, but can still be a precursor of other coronary events which are caused by rupture of an atherosclerotic plaque. One year mortality of 1.4% in the invasive group and 2.3% in the conservative group (p = ns) indicate low overall mortality in those patients who survived the 14 days to perform exercise. There was an increase in mortality in those patients who did not perform exercise, but this would presumably include the early deaths. The TIMI II study (Zaret BL et al. 1995) also found that both rest and exercise radionucleotide ejection fraction in 2,567 patients were important prognostic indicators of one year survival.

One hundred and ninety patients from TAMI 1 and 111 studies who did not undergo immediate PTCA following thrombolysis were studied to determine the relationship between morphology of the infarct related artery post thrombolysis and in hospital ischemic events: Cardiac death, Recurrent ischemic pain requiring emergency CABG or PTCA or reocclusion of infarct related artery at repeat angiography (Ellis SG et al. 1989). 21% of patients had recurrent ischemic events but they could not be predicted by any anatomical variables from the initial angiogram. A further study of the effect of infarct artery status on clinical outcome in 50 patients showed that residual stenosis of >50% of the infarct related vessel, TIMI 2 reperfusion grade(ie sub optimal flow), intermittent patency in combination predicted reocclusion. Residual stenosis of the infarct related artery was associated with a significant increase in number of in hospital ischemic events (Grines CL et al. 1988).

		Total N=1,168	ST ↓ N=127 (%)	No ST ↓ N=1,041 (%)	P Value
No of vessels ≥ 60%	0	115	5(4.4)	110(11.7)	0.001
	1	642	60(52.6)	582(61.7)	
	2	243	32(28.1)	211(22.4)	
	3	57	17(14.9)	40(4.2)	0.001
Infarct related artery IRA	RCA	490	66(55.9)	424(43.6)	
	LAD	463	26(22)	437(44.9)	
	Cx	136	26(22)	110(11.3)	0.001
Mean % stenosis		75.0	77.9	74.6	0.09
TIMI grade	0	117	17(15)	100(10.9)	
	1	24	2(1.8)	22(2.4)	
	2	99	16(14.2)	83(9)	
	3	794	78(69)	718(77)	0.14
Collaterals to IRA	yes	121	15(13.2)	106(11.2)	
	no	936	99(86.8)	837(88.8)	0.54
PTCA performed	yes	719	66(52)	653(62.7)	
	no	449	61(48)	388(37.3)	0.02

Table 3.5 The relationship between exercise induced ST segment depression and the findings of cardiac catheterisation (modified from TIMI II)

4. METHODS

4.1 Admission to Coronary Care Unit

Between 1988 and 1992 two hundred and twelve patients were recruited to this study. All patients were admitted to the Coronary Care Unit, Stobhill General Hospital by three possible routes. Firstly, by direct admission to the Coronary Care Unit referred by local General Practitioners using a separate phone line. This facilitated early admission via the "back door" for patients with suspected acute myocardial infarction and significantly reduced the "door-to-needle" time in the administration of thrombolytic therapy. Secondly, patients were referred by middle grade medical staff in the usual way from the Accident & Emergency Department. Thirdly, patients were transferred from other wards within the hospital if they sustained an acute myocardial infarction during an in patient stay for other medical conditions.

On admission to Coronary Care, all patients had a clinical history, examination and ECG performed prior any therapeutic intervention. Once the diagnosis of acute myocardial infarction was made, standard therapies of aspirin, oxygen and opiate analgesia were administered unless there were specific contraindications. IV nitrates were given if clinically indicated at the discretion of the medical Registrar in attendance. With reference to the absolute and relative contraindications for thrombolysis, a decision was made as to whether the patient was a candidate for this treatment. If the patients were suitable for thrombolysis they were then considered for inclusion in one of the four studies outlined below. The Cardiology Registrar and Consultant on-call for thrombolysis research were contacted. The patient's suitability for current research study was then assessed immediately. The risks and benefits of the study were carefully explained to the patient and any attending relatives. An information sheet was issued, written informed consent was obtained. An example of the Patient Sheet and accompanying Consent Form are shown Appendix III.The patient was then entered into one of the four studies outlined below, once the inclusion and exclusion criteria specific for each study had been met.

4.2 Thrombolytic Studies

The 4 separate studies are outlined briefly below. Full description of the individual studies are outlined in appendix I and II

4.2.1 Study 1:Anisterpilase 30 U v Streptokinase 1.5 MU

128 patients were included in a randomised, controlled, double-blind, double-dummy study of 30 U of anistreplase vs 1.5 MU of Streptokinase. The primary endpoint of the study was to compare angiographic patency rates at 90 mins and 24 hrs by TIMI scoring following therapy. 1.5MU of Streptokinase was given intravenously over 1 hour and 30 U anistreplase given as an i.v. bolus over 5 mins.

4.2.2 Study 2:Bolus administration of rTPA 2 x 35mg

33 patients were recruited to an open study to determine the efficacy of 2 x 35 mg boluses of Tissue Plasminogen Activator (TPA) given at 30 min intervals. The primary endpoint was similar to that of study 1, ie angiographic patency at 90 mins and 24 hrs following therapy.

4.2.3 Study 3:Bolus administration of rTPA 3 x 20 mg

21 patients recruited in open evaluation of the efficacy of three 20mg bolus doses of TPA given at an interval of 10 mins between doses. The endpoint of this study was angiographic patency at 45, 60 and 90 mins and 24 hrs post therapy. For the purpose of this study to allow direct comparison with the other studies. Only angiographic patency at 90 mins and 24 hrs were considered in the final analysis.

4.2.4 Study 4:Comparison of 3 bolus regimes of rTPA

31 patients in a randomised open study comparing three regimes of double bolus TPA given at an interval of 30 mins between boluses (a) 50 mg, followed by 50 mg, (b) 20 mg, followed by 50 mg, (c) 20 mg followed by 50 mg. The primary endpoints of this study were to assess patency at 90 mins and 24 hrs.

4.3 Acute Angiography

Time from onset of symptoms of acute myocardial infarction to administration of thrombolysis was noted. Following treatment, angiography was performed in an area adjacent to the main Coronary Care Unit, to define patency at the time points outlined above. In all cases the right femoral artery was used for arterial access. Coronary angiography was performed using the standard Judkins's technique. A mobile x-ray Image Intensifier with a television display (SIREMOBIL 2N-2H) and a circular arm allowing rotation about the horizontal axis, was used to obtain standard angiographic views. The right coronary artery, visualised in a 60° LAO and a 30° RAO projection. The left anterior descending and circumflex arteries were visualised in a 10° RAO, a 30° RAO and a 60° LAO projection. A left ventriculogram was performed following the 24 hr angiogram however the results of this investigation was not considered in this present study. This unit was linked to a heavy duty video cassette recording system (JVC CR-8200E) which allowed permanent recordings of coronary angiograms and left ventriculograms. Each angiogram was performed by a Consultant Cardiologist assisted by a Cardiac Registrar. Further assistance was provided by the Coronary Care Nursing Staff. The Image Intensifier was operated by a Radiographer and an ECG Technician was present to record intra-arterial pressures and monitor the electrocardiogram during the procedure. Conventional Seldinger technique was used and a number 7 Sheath (Hemaquet, USCI International) inserted in the right femoral artery. On the basis of the infarct site on the admission ECG the presumed infarct related artery was cannulated first to determine patency. The non infarct related arteries were then visualised to define additional vessel disease. Following acute angiography, the sheath was flushed with heparin and left in situ for 24 hrs. Four hours after thrombolysis intravenous heparin was given as a 5000 U bolus followed by a continuous infusion of 1000 U/hr to achieve anticoagulation. The APPT was maintained between 2-3x the control value by dose adjustment of the continuous heparin infusion. Heparin was discontinued 30-60 mins prior to a second angiogram at 24 hrs. The sheath was removed once the coagulation status had reverted to normal following the second angiogram.

Antibiotics, mainly cephalexin 500 mg tid were given as prophylaxis during the time that the sheath was in situ.

4.4 Patient Selection

All patients presenting at the Coronary Care Unit with suspected diagnoses of acute myocardial infarction were considered for thrombolytic therapy if they fulfilled the following criteria:

1. The onset of symptoms of myocardial infarction lasting ≥ 30 mins and ≤ 6 hrs by the time of admission to the Coronary Care Unit.
2. Confirmatory electrocardiographic evidence of acute myocardial infarction with ST segment elevation ≥ 1 mm in at least two standard limb leads, or ≥ 2 mm ST elevation in at least two contiguous precordial leads.
3. Absence of standard contraindications for thrombolysis to limit the potential side-effects of this therapy.

Entry into the ongoing research study required additional entry and exclusion criteria outlined in appendix I and II..

Severe peripheral vascular disease or physical disability preventing coronary angiography, were exclusion criteria for entry into the study, but not a contraindication to thrombolysis. Patients with a previous myocardial infarction were eligible for the studies if the ECG changes of acute ST segment elevation were present in a new infarct territory.

4.5 Clinical characteristics

The following clinical characteristics were recorded for each patient , and used to predict the result of the predischarge exercise test and outcome during the 5 years of clinical follow up:

Age was used as a continuous variable but patients were also divided into 2 group based on the median age to facilitate analysis of categorical data and prediction of future cardiac events.

Sex was compared in analysis of all data.

Infarct site was defined by the location of diagnostic ST segment elevation on the ECG on admission to the coronary care unit and categorised as follows:

1. Anterior:V1-V6
2. Inferior :II, III, aVF
3. Lateral: Isolated changes in V5 and V6 or lead I and aVL

Reciprocal Depression on the admission ECG was defined as coexistent horizontal or downsloping ST segment depression of ≥ 1mm 80msec after the j point in the non infarct territory.

Time to Thrombolytic therapy from onset of symptoms was noted. The entry criteria for all the research studies stipulated that thrombolysis had to be given within 6 hrs of the onset of symptoms. For the purpose of this analysis the patients were divided into 3 subgroups according to time to treatment: 0-2hrs, 2-4hrs and 4-6hrs.

4.6 Coronary Patency

The artery presumed to be the infarct-related artery from ECG changes on admission to Coronary Care, was visualised first during angiography at 90 min. Patency was defined by the TIMI scoring (Appendix IV). A score of 0 or 1 was considered as non-patent and a score of 2 or 3 considered as patent. Patency was reassessed angiographically at 24 hrs by the same scoring system. All angiograms were analysed blind by two experienced Consultants. If their interpretation was different, a consensus of opinion was reached

following discussion. The effect of TIMI score 0-3 on the results of exercise testing and clinical outcome were considered as four distinct groups. TIMI scores were then combined by defining patency as TIMI score 2 or 3 and non patency as 0 or 1. The effect of patency on the results of exercise testing and clinical outcome could then be assessed. The predictive value full patency TIMI score 3 was compared against the combination of TIMI scores 0,1 and 2. Coronary artery patency of the infarct-related vessel was further assessed by combining the TIMI scores from both angiographic assessments defining time to patency as outlined below in Table 4.1.

Time Score 90 mins	Time Score 24 hrs	Group
(2,3)	(2,3)	Early Patency (EP)
(0,1)	(2,3)	Late Patency (LP)
(0,1)	(0,1)	Non Patent (NP)
(2,3)	(0,1)	Reocclusion (R)

Table 4.1 Time to Patency Groups

4.7 Residual Stenosis

Residual stenosis of the infarct related artery was defined following the angiogram at 24 hrs by the TIMI scoring system for coronary stenosis (appendix V). A significant stenosis was considered as 50-90% (score 2). However a stenosis of 90-99% with complete or incomplete filling (score 3 and 4 respectively) were categorised qualitatively as a significant stenosis and not considered as separate sub groups for the purpose of this present study. A total occlusion (score 5) of the infarct related artery was considered as a distinct subgroup and compared against no stenosis (<50%,score 1) and significant stenosis (50-99%,score 2-4). Following cannulation of the infarct-related vessel, the other coronary artery was visualised to define additional vessel disease. A similar scoring system was used to define significant stenosis of additional vessels. Firstly the effect of residual stenosis or occlusion of the infarct related artery on the results of exercise testing and clinical outcome was considered regardless of additional vessel disease. Patients with no significant stenosis of

the infarct related artery and no additional vessel disease were considered as single vessel disease not 0 vessel disease The effect of stenosis or occlusion in single vessel disease was considered as a separate sub group.

4.8 Multivessel Disease

The influence of single , double and triple vessel disease on the results of exercise testing and clinical outcome was studied. The influence of triple vessel disease was further assessed by comparing it against a combination of single and double vessel disease.

4.9 Pre-discharge Exercise Testing

The arterial sheath was removed when satisfactory haemostasis had been established by measurement of the APPT after the 24 hr angiogram. Patients were then mobilised in the usual way post-infarct under the supervision of the nursing and physiotherapy staff involved with cardiac rehabilitation. Prior to discharge from hospital (7-33 days, mean 12 days) patients underwent a symptom-limited exercise test on a motorised treadmill using the modified Bruce protocol. It was general policy to treat patients prior to exercise testing conservatively, but the prescription of medication was at the discretion of the Consultant Cardiologist responsible for the patient's care. The exercise test was terminated for one of the following reasons:

1. **Symptoms** of angina, breathlessness, fatigue or other symptoms such as leg pain which prevented continuation of exercise.
2. **ST depression** ≥ 3 mm Downsloping or horizontal, 80 m.secs after the J point.
3. **ST segment elevation** in the non-infarct territory.
4. **Fall in blood pressure** of ≥ 20 mmHg in the previous stage of exercise.
5. Achievement of an age-predicted **maximum heart rate** (200 -age).

Prior to the exercise test a resting 12 lead ECG was performed and blood pressure measured manually. The exercise test was performed using a Quinton motorised treadmill with continuous ECG monitoring in 3 leads (AVF, V_1 and V_5). A modified Bruce protocol (Appendix VI) was used. Hard copy 12 lead ECG was produced at rest, at the end of each 3 min stage and at 3 min intervals into the recovery phase for a period of time depending upon the exercise response. Blood pressure was measured manually immediately at the end of the exercise test

4.9.1.1 Exercise Variables

The following exercise variables were obtained from analysis of the hard copy summaries of the exercise test:

1. The development of **ST segment depression**, downsloping or horizontal ≥ 1 mm, 80 secs after the J point in two contiguous leads.
2. The development of **ST segment elevation** ≥ 1 mm in two contiguous limb leads or ≥ 2 mm after the J point in the precordial chest leads, 80 m.secs after the J point.
3. **T wave normalisation** defined as any negative deflection of the T wave in the infarct territory which becomes isoelectric or positive during exercise.
4. **Systolic blood pressure** was measured at rest and at peak exercise. Patients were divided into 2 groups depending on whether they achieved a rise in systolic blood pressure of ≥ 30mmHg.
5. **Rate pressure product** at rest and at peak exercise. Median rise in rate pressure product was calculated and patients were divided into 2 groups depending on whether they achieved the median rise in rate pressure product.
6. Any **symptoms** occurring during exercise. All reported symptoms were combined to compare symptomatic versus asymptomatic patients. Patients who were asymptomatic either reached target heart rate for their age or were stopped by the operator because of ECG or Blood pressure abnormalities on the exercise ECG. **Angina** reported during the exercise test was also considered separately in the analysis.

7. **Total Exercise time** in secs was recorded.
8. **Metabolic equivalents** at peak exercise.

4.10 Clinical follow up

Patients were followed up for a variable period of time at the outpatient clinic of one of the three Consultant Cardiologists. Intervention was on clinical grounds and not on the results of the angiogram at the time of acute myocardial infarction. Medication again was introduced on symptomatic grounds on clinical judgement of the Physician in attendance at the Outpatient Clinic. Five years after the administration of thrombolytic therapy, case-notes were reviewed to determine retrospectively which patients experienced cardiac events. Clinical data,the results of the angiogram performed at 90 mins and 24 hrs and the pre-discharge exercise test variables were related to clinical outcome.

4.11 Cardiac Events

For the purpose of this study, three time points were identified:

1. ***In-hospital cardiac events*** occurring after angiography at 90 mins to discharge from hospital.
2. ***Outpatient cardiac events*** occurring from hospital discharge to 5 years.
3. ***Overall cardiac events*** which combined in-hospital and outpatient events.

Events were considered as primary or secondary. Primary events were considered as likely to result in alteration of underlying coronary anatomy and potentially influence prognosis. Secondary events were thought to occur as a result of coronary anatomy defined following the initial invasive assessment. A patient could have a secondary event recorded and then experience a primary event. However once a primary event was recorded the patient was censored from further survival analysis and further primary or secondary events were not entered.

The exception to this rule was overall mortality from sudden cardiac death. which was analysed separately from other end points regardless of a previous primary or secondary events such as recurrent myocardial infarction. It was also included in the analysis of all combined cardiac events as a single primary endpoint resulting in censorship of further events as described above.

Primary Events

1. Unstable Angina
2. Recurrent Myocardial infarction
3. Revascularisation with PTCA or CABG
4. Sudden Cardiac Death

Secondary Events

1. Peri infarct acute left ventricular failure
2. Congestive cardiac failure as an outpatient
3. Post Infarct Angina

4.11.1 Inhospital Events

4.11.1.1 Cardiac pain occurring post-infarct (unstable angina).

complaining of cardiac sounding chest pain at rest or on ward ambulation for ≥ 10 min with or without accompanying ECG changes occurring in the peri infarct period following thrombolysis or during the period of in hospital admission. This was a primary endpoint.

4.11.1.2 Peri-infarct acute left ventricular failure.

Acute left ventricular failure (ALVF) was defined as symptoms of breathlessness at rest accompanied by one of the following signs:

Sinus tachycardia
Third Heart Sound
Basal Crepitations to Mid zone

An entry in the case record by the cardiology consultant or registar confirming this clinical diagnosis was required. Radiological documentation was sporadic and dependent on the attending physician and was not used to define ALVF. This was a secondary end point allowing the patient to continue in the survival analysis until the first primary end point was recorded. It was not incorporated as a cardiac ischemic event and analysed separately

4.11.1.3 All cardiac ischemic events

1. Cardiac pain occurring post infarct
2. In hospital Mortality
3. Recurrent myocardial infarction
4. Emergency PTCA
5. Emergency CABG

The numbers of individual events in categories 2-5 were very small and could not be analysed seperately. They were therefore combined to define a cardiac ischemic event. However only primary cardiac events were recorded and thus angina and heart failure post infarct were not included in this group.

4.11.2 Outpatient Cardiac Events

4.11.2.1 Post-infarct angina

Angina reported to the attending physician during outpatient follow up was recorded from the retrospective review of the outpatient letters from the case sheet. A diagnostic exercise test was not required. Post infarct angina was considered a secondary end point and considered in isolation from the other primary ischemic endpoints.

4.11.2.2 Post Infarct Congestive Heart Failure

A diagnosis of congestive cardiac failure recorded in the case sheet by the attending consultant physician was required to register an event in this category. Documentation of clinical signs was variable as was non invasive investigations such as chest x ray or

echocardiography and therefore not required to record congestive cardiac failure as an event. No analysis of medication for congestive heart failure was made. This study predated the widespread use of ACE I .An analysis of diuretic treatment would have been useful but extraction of accurate data from the outpatient letters proved very difficult. Outpatient Congestive Cardiac Failure was considered a secondary end point and considered in isolation from the other primary ischaemic endpoints.

4.11.2.3 All Cardiac Ischemic Events

The frequency of individual primary cardiac ischaemic events outlined in bold below was low and therefore all events were combined in this analysis.

1. A diagnosis by the consultant of Post infarct **Unstable Angina** requiring hospitalisation with or without ECG changes in the case sheet.
2. **Recurrent myocardial infarction** requiring 2 of the following 3 criteria 1) Diagnostic ECG changes of ST Elevation > 1mm or pathological T Wave Inversion 2)chest Pain or symptoms consistent with Myocardial Infarction 3)a serial rise in Cardiac enzymes (CK AST LDH)
3. Revascularisation by **PTCA or CABG** on symptomatic or prognostic grounds. Patients were not referred on prognostic grounds on the basis of the results of the peri infarct angiograms and therefore usually required on going symptoms of angina and repeat diagnostic angiography.
4. Documentation of **Sudden Cardiac Death** occurring following a further admission to hospital or the A/E department from arrhythmia or end stage congestive heart failure was required to record this event. Death from non cardiac causes was recorded but not used in the analysis unless specifically indicated. Deaths at home not documented in the case record were defined as non cardiac. No attempt was made to analyse death certificate data and therefore some of these deaths may have been cardiac in nature an the total no of cardiac deaths underestimated over the 5 yr period.

4.11.3 Overall Cardiac Events

Inhospital cardiac events were combined with out of hospital events to define overall events using the criteria described above for primary and secondary endpoints

4.11.3.1 All cardiac ischemic events

1. Ischemic pain post infarct
2. Unstable angina
3. Recurrent myocardial infarction
4. PTCA or CABG
5. Sudden Cardiac Death

4.11.3.2 Heart failure overall

1. Peri infarct Acute Left Ventricular Failure
2. Out patient congestive cardiac failure

   both of these events were secondary end points

4.11.3.3 Mortality.

Mortality during both inpatient and out patient follow up were combined as described above primary events such as recurrent myocardial infarction were allowed to occur an mortality still recorded as a primary end point.

4.12 Statistical Analysis

Categorical variables were analysed using Chi squared analysis with MINITAB computer Software converting to a P value using chi squared tables. Continuous variables were analyse using ANOVA with MINITAB computer Software. Where appropriate continuous variables were converted to categorical variables to facilitate group analysis for example the median total exercise time was calculated and used to define 2 groups of patients those who failed to achieve median exercise time and those who achieved median exercise time or more. A macro program operating within MINITAB was written to facilitate this analysis. To determine the predictive value of the results of angiography and exercise

testing on cardiac events. Kaplan Meir event-free survival analysis was used with an SPSS software package, comparing the groups with a log rank test. Finally to determine the independent predictors of clinical outcome a multivariate analysis was performed using Cox Regression with SPSS software package. In all statistical test significant levels were defined $P < 0.05$ however p values not quite achieving statistical significance are described as a trend.

4.13 Aims and Objectives

The results of Exercise testing, post myocardial infarction has been shown in the pre-thrombolytic era to be predictive of future cardiac events. Recent studies have reassessed the usefulness of the exercise test following thrombolysis and have shown reduced sensitivity, specificity and predictive accuracy for the exercise test in the prediction of future ischaemic events or cardiac death. However, no study has attempted to correlate the early angiographic assessment (90 min and 24 hrs) of coronary artery patency of the infarct related artery following thrombolysis and additional coronary artery disease, with the results of symptom limited pre-discharge exercise testing and long term clinical follow up.

5. EXERCISE TESTING

5.1 Patient Characteristics

The demographic characteristics of the 212 patients, listed below, in this study who received thrombolysis within 6 hrs of the onset of symptoms of myocardial infarction, were analysed to determine whether they predict the results of predischarge Exercise Testing and clinical outcome.

1. Age
2. Sex
3. Infarct Related Artery
4. Site of Infarct
5. Reciprocal Depression
6. Time to Treatment

5.1.1 Age

The mean age was 55.9±9.1 yrs ,the age range 31-74 yrs and the median age 56 years. Patients were divided into 2 groups based on the median age of 56 yrs to facilitate analysis of categorical data. The influence of age on the results of exercise testing by ANOVA is shown below in Table 5.1. As shown, patients achieving less than median workload of 5.8 mets were significantly older (57.8 ± 8.1 yrs versus 52.3 ± 9.5 yrs, $p < 0.001$). This is illustrated in fig 5.1. There was no relationship between age and other exercise variables. The influence of age on clinical outcome in terms of in-hospital events ,out-patient events and overall events is summarised below in Tables 5.2, 5.3 and 5.4 respectively. As shown by event free survival analysis, patients older than the median age of 56 yrs had a increased mortality (16% v 6%,$p = 0.023$). There was a trend towards a greater incidence of outpatient cardiac events (41% v 34%,$p = 0.054$) and total cardiac events (50 % v 42%,$p=0.061$) in older patients compared to those ≤ the median age. This is illustrated in fig 5.2.

	Age (mean)	SD	P value
Exercise Time			
< 540 sec	55.5	8.2	
≥ 540 sec	53.7	9.9	0.227
Metabolic Equivalents			
< 5.8	57.8	8.1	
≥ 5.8	52.3	9.5	**0.001**
Change in Double Product			
< 8500	56.2	7.8	
≥ 8500	54.9	11.2	0.662
Change in Systolic B.P.			
< 30 mmHg	55.3	8.5	
≥ 30 mmHg	55.9	11.4	0.834
Symptoms			
Asymptomatic	54.3	9.8	
Symptomatic	54.6	8.5	0.831
No Angina	54.4	9.3	
Angina	54.8	9.0	0.848
ST-T Changes			
No ST ↓	53.7	9.8	
ST ↓	55.7	8.0	0.191
No ST ↑	54.4	9.4	
ST ↑	54.7	8.7	0.835
No T ↓	54.6	9.3	
T ↓	54.2	9.2	0.785

Table 5.1 Age and Exercise Variables

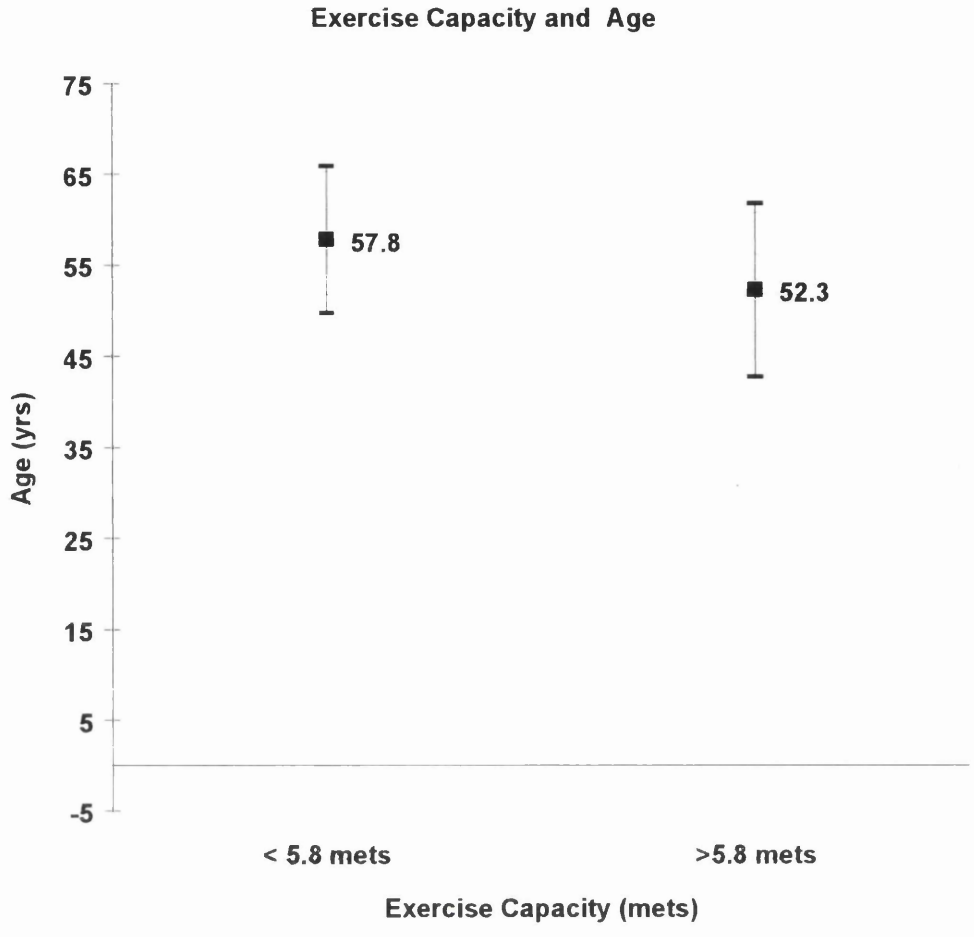

Figure 5.1 Exercise Capacity and Age

	Age	Total Patients	Total Events	%	P Value
Ischemic Pain	<56 yrs	99	9	9	
	≥56 yrs	106	10	9	0.890
Acute LVF	<56 yrs	99	10	10	
	≥56 yrs	106	16	15	0.227
All Cardiac Events	<56 yrs	99	14	14	
	≥56 yrs	106	20	19	0.351

Table 5.2 Age and in Hospital Cardiac Events

	Age	Total Patients	Total Events	%	P Value
Angina	<56 yrs	99	38	39	
	≥56 yrs	106	38	36	0.894
Heart Failure	<56 yrs	99	20	20	
	≥56 yrs	106	22	21	0.918
All Cardiac Events	<56 yrs	99	34	34	
	≥56 yrs	106	44	41	**0.054**

Table 5.3 Age and Outpatient Cardiac Events

	Age	Total Patients	Total Events	%	P value
Mortality	<56 yrs	99	6	6	
	≥56 yrs	106	17	16	**0.023**
Heart Failure	<56 yrs	99	27	30	
	≥56 yrs	106	32	30	0.614
All Cardiac Events	<56 yrs	99	41	42	
	≥56 yrs	106	52	50	0.061

Table 5.4 Age and Overall Cardiac Events

Fig 5.3 shows the Kaplan Meier cumulative survival curve for patients < or ≥ the median age of 56 yrs. Patients of ≥ 56 yrs had a significant increase in mortality (p=0.023).

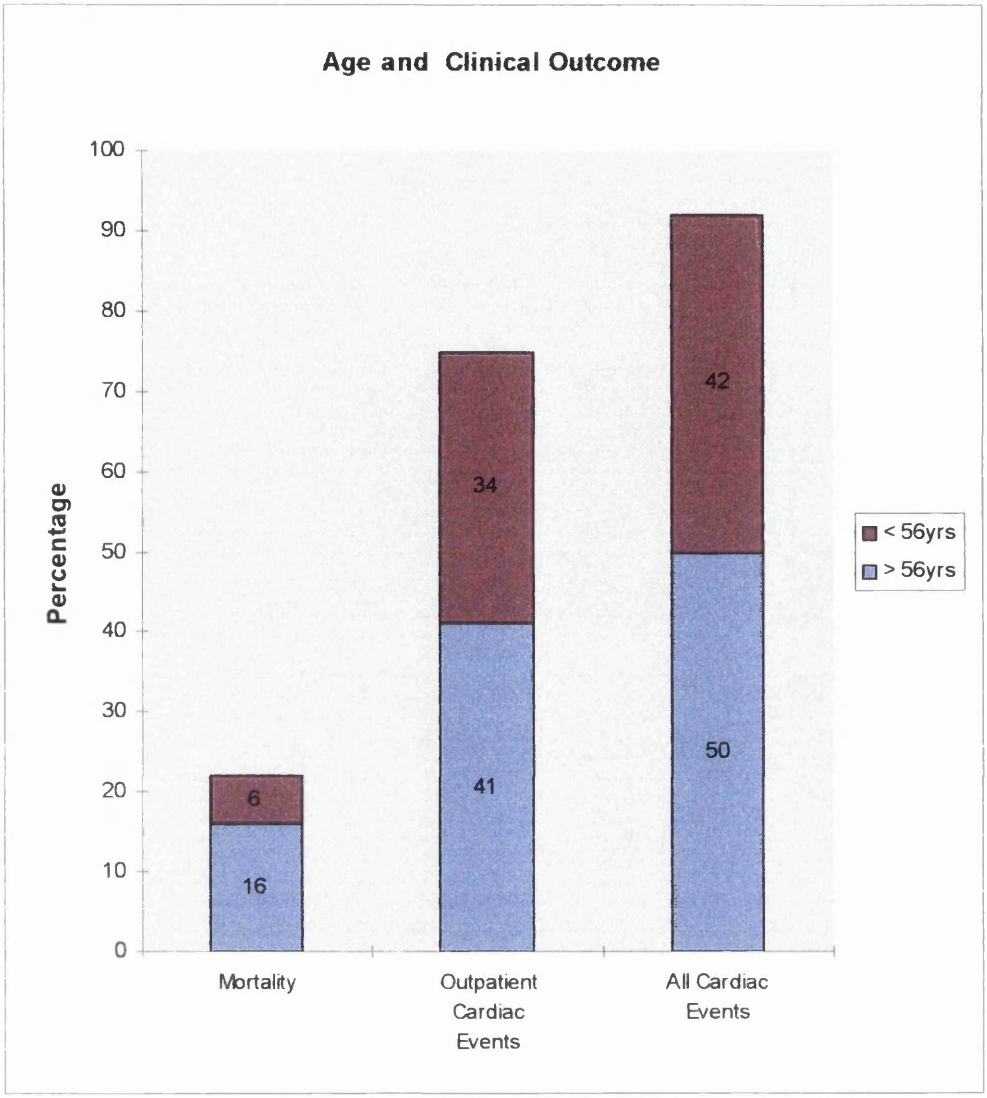

Figure 5.2 Age and Clinical Outcome

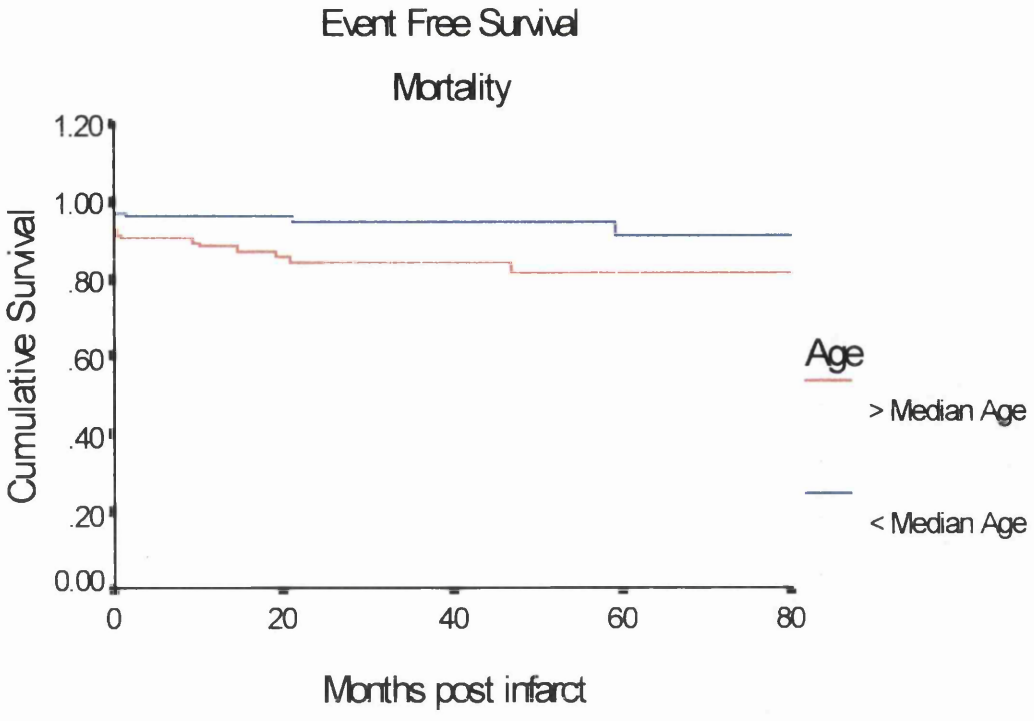

Figure 5.3 Age and Mortality

5.1.2 Sex

The distribution of males and females and respective ages in the study is shown in below in table 5.5

	Number	%	Age Mean ± SD	P Value
Males	161	76	54.4 ± 9	
Females	51	34	60.5 ± 8	**0.001**

Table 5.5 Age and Sex Distribution

The study population contained 34% females who were significantly older. The influence of sex type on the results of exercise testing by chi squared analysis, are summarised in Table 5.6. This table is constructed to show the true positive data ie. the number of males and females with the abnormal exercise variable. The total number of patients exercised who had the abnormal exercise response can be calculated from the percentage figures quoted. The total number of males or females in whom the exercise variable was recorded can be similarly calculated from the percentage figures in parenthesis for each sex type. This avoids presentation of the whole chi squared table for each variable. A total of 145 patients were exercised. Some exercise variables such as Systolic Blood pressure response were not well recorded resulting in missing data and reduced numbers of observed counts.

The influence of sex on clinical outcome over 5 yrs is shown in tables 5.7 ,5.8 and 5.9. As shown in, 40% of males reported symptoms during the exercise test, compared to 17% of females ($p < 0.05$). This is illustrated in Fig 5.4. More males reported angina during exercise testing but this was not statistically significant. Chi squared analysis requires at least five expected counts in each cell. Therefore as only 1 female complained of angina during exercise this statistical method is invalidated. Sex did not affect the incidence of in-patient, outpatient or overall cardiac events over the 5 yr. follow up period.

Exercise Variables n = (% Total)	Male n=(%Total)	Female n=(%Total)	X^2	P value
Exercise Time < 540 sec n = 69 (44)	57 (46)	12 (38)	0.739	NS
Workload < 5.8 mets n = 71 (50)	55 (49)	16 (53)	0.169	NS
Δ In Double Product<8500 n = 23 (48)	15 (42)	8 (66)	2.254	NS
Δ In Systolic BP < 30 mmHg n =30 (62)	21 (58)	9 (75)	1.067	NS
Symptomatic n = 71 (46)	50 (40)	21 (17)	6.567	**< 0.05**
Angina n =19 (12)	18 (14)	1 (3)	3.086	NS
ST Depression n =60 (38)	50 (40)	10 (31)	0.885	NS
ST Elevation n =42 (27)	37 (30)	5 (16)	2.682	NS
T Normalisation n = 65 (41)	51 (41)	14 (43)	0.072	NS

Table 5.6 Sex and Exercise Variables

	Sex	Total Patients	Total Events	%	P Value
Ischemic Pain	Male	161	17	10	
	Female	51	4	7	0.539
Acute LVF	Male	161	21	13	
	Female	51	7	14	0.897
All Cardiac Events	Male	161	28	17	
	Female	51	8	16	0.700

Table 5.7 Sex and in Hospital Events

	Sex	Total Patients	Total Events	%	P Value
Angina	Male	161	54	24	
	Female	51	24	47	0.126
Heart Failure	Male	161	32	19	
	Female	51	11	21	0.986
All Cardiac Events	Male	161	62	39	
	Female	51	17	33	0.728

Table 5.8 Sex and Outpatient Cardiac Events

	Sex	Total Patients	Total Events	%	P Value
Mortality	Male	161	18	9	
	Female	51	5	9	0.995
Heart Failure	Male	161	46	27	
	Female	51	16	32	0.950
All Cardiac Events	Male	161	75	47	
	Female	51	21	41	0.441

Table 5.9 Sex and Overall Cardiac Events

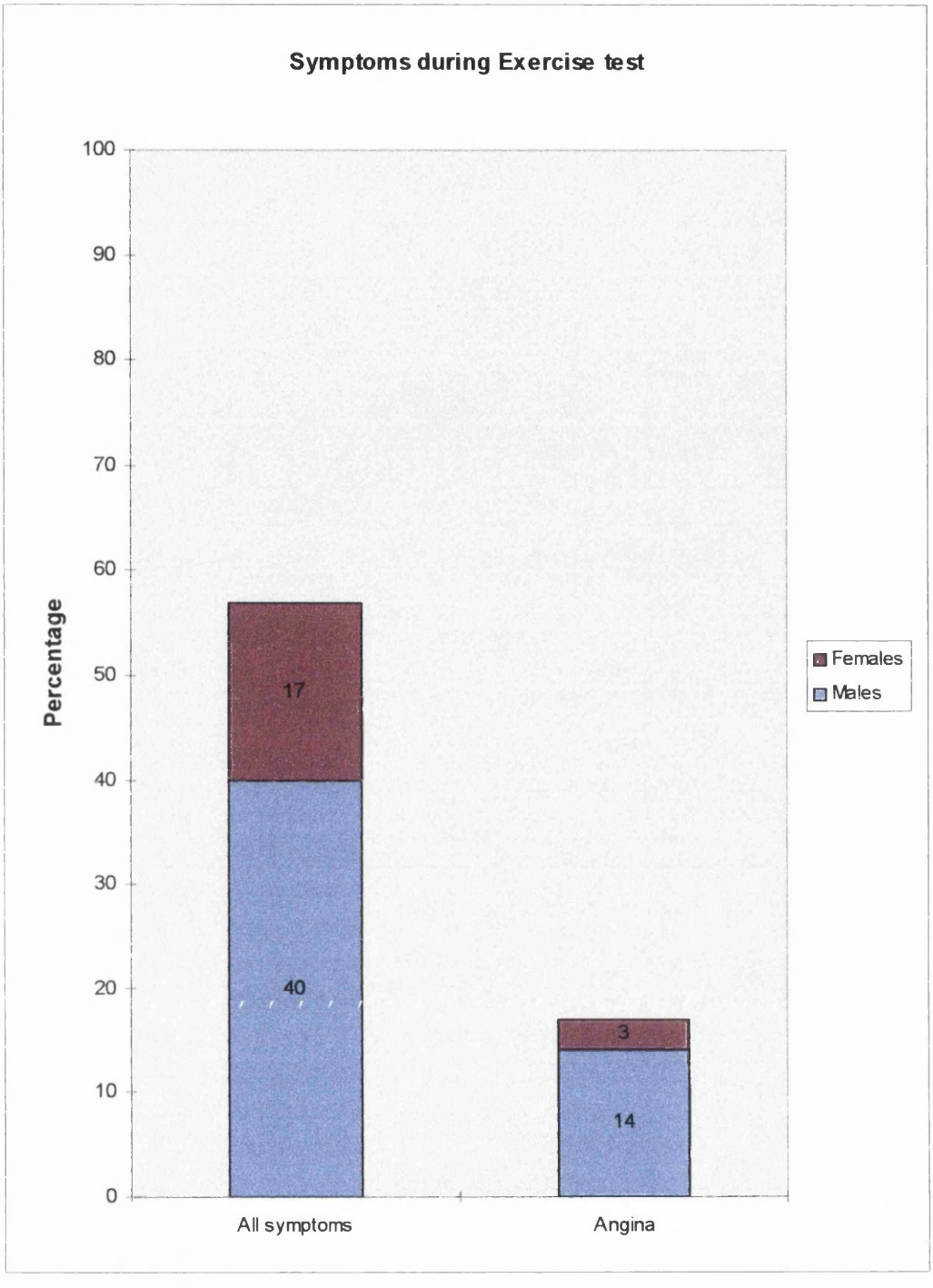

Figure 5.4 Sex and Symptoms during Exercise

5.1.3 Infarct Related Artery

The infarct related artery was identified at angiography 90 min following treatment with thrombolysis. Table 5.10 shows the distribution of the infarct-related artery of patients in the study.

Infarct related artery	n	%
RCA	94	47
LAD	91	45
Cx	15	7

Table 5.10 Infarct Related Artery

In 12 patients angiography could not be performed and therefore the infarct related artery could not be defined. Only 15 patients had circumflex as the infarct-related artery. The numbers of events in this case was not sufficient to allow statistical analysis and this group was omitted allowing direct comparison between RCA and LAD arteries.

The relationship between the infarct-related artery and the results of the exercise testing is shown in Table 5.11. The construction of this table is similar to fig 5.6. Patients with a LAD occlusion had a reduced exercise capacity compared to those with RCA with more failing to achieve a median workload of 5.8 metabolic equivalents in the exercise test (62% v 40%,$p<0.05$). This is illustrated in Fig 5.5. There was an increased incidence of ST segment depression during exercise in patients with RCA compared to LAD as the infarct related vessel (48% v 27% $p< 0.05$). This is illustrated in Fig 5.6. However, ST segment elevation during exercise was almost exclusively seen in patients with LAD compared to RCA as the infarct related artery (47% v 8%,$P<0.001$). However T wave normalisation did occur in patients with RCA occlusions but was significantly more common with LAD as the affected artery (33% v 55%,$p<0.05$). The relationship between ST-T changes and infarct related artery is illustrated in Fig 5.6. The effect of infarct-related artery (LAD versus RCA) on in-hospital, outpatient and overall events are summarised in tables 5.12,

5.13. and 5.14. As shown, patients with LAD compared to RCA as infarct related artery had a significantly higher incidence of peri-infarct acute left ventricular failure (20% v 6%,$p<0.003$). This is illustrated by Kaplan Meier event free survival analysis in Fig 5.7. The LAD as infarct related artery compared to RCA was more likely to result in heart failure as an outpatient(28% v.13%, $p=0.014$) and overall heart failure (44% v 16%, $p=0.001$). The Kaplan Meier event free curves are illustrated in Fig 5.8 and Fig 5.9 respectively.

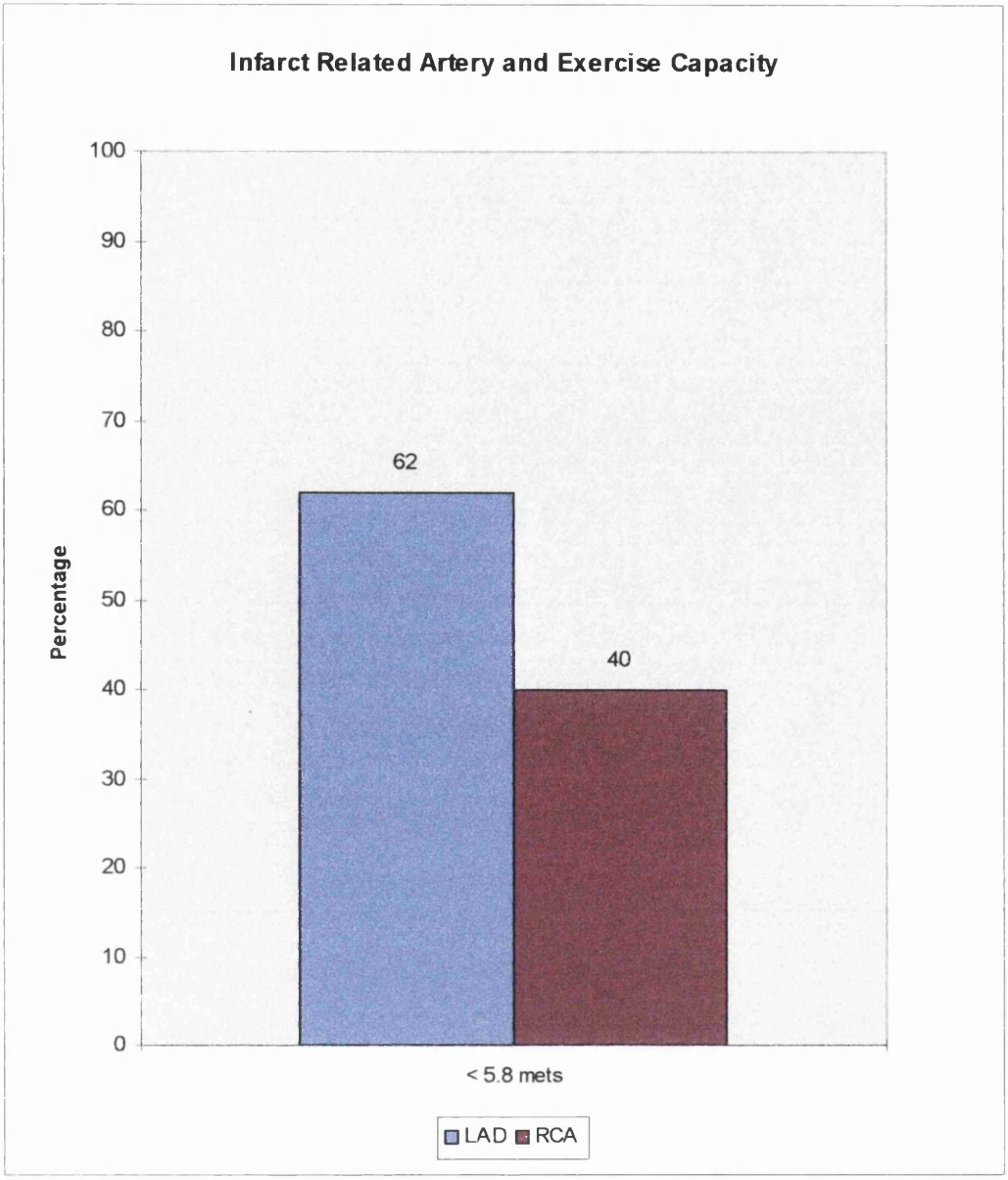

Figure 5.5 Exercise Capacity and Infarct Related Artery

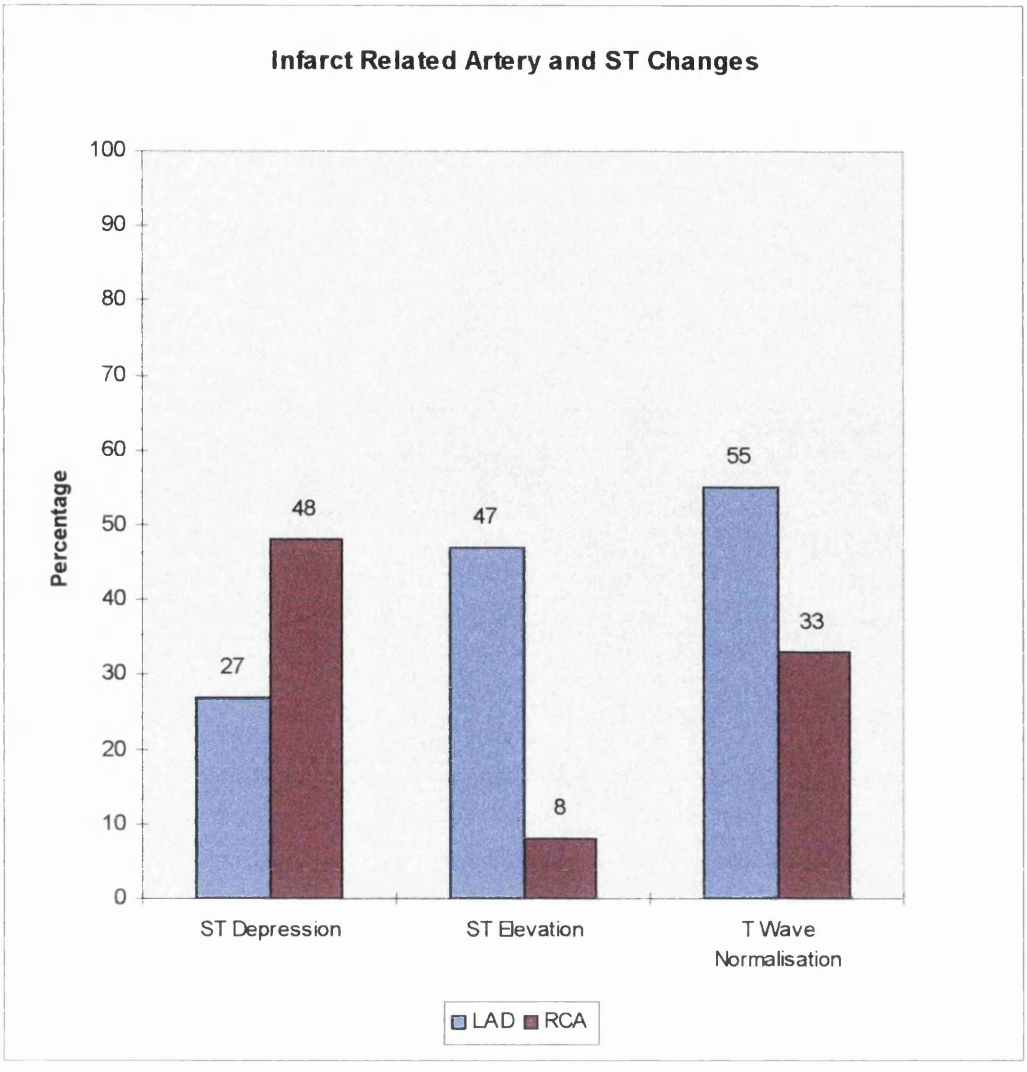

Figure 5.6 Infarct Related Artery and ST Changes

Exercise Variables n = (% Total)	LAD n =(%Total)	RCA n= (%Total)	χ^2	P value
Exercise Time < 540 sec n = 64 (45)	36 (51)	28 (39)	2.045	NS
Workload < 5.8 mets n = 66 (52)	40 (62)	26 (40)	6.131	**<0.05**
Δ Double Product < 8500 n = 22 (51)	11 (61)	11 (44)	1.226	NS
Δ Systolic BP < 30 mmHg n = 30 (70)	15 (83)	15 (60)	2.701	NS
Symptomatic n = 63 (44)	34 (49)	29 (40)	0.851	NS
Angina n = 16 (11)	7 (10)	9 (13)	0.251	NS
ST Depression n = 53 (37)	19 (27)	34 (48)	6.466	**< 0.05**
ST Elevation n = 39 (28)	33 (47)	6 (8)	25.91	**< 0.001**
T Normalisation n = 63 (45)	39 (55)	24 (33)	6.847	**< 0.05**

Table 5.11 Infarct Related Artery and Exercise Variables

5.1.4 Site Of Infarct

It was possible to identify the site of infarct from the original ECG in 193 of the 212 patients(91%). Table 5.15 shows the distribution of anterior, inferior and lateral infarcts in the study. Only 5 patients (2.5%) had isolated ST segment elevation in V5 and V6 or I and aVL defining a lateral infarct. The small number of observations in this group invalidated the statistical analysis and lateral infarcts were omitted allowing direct comparison between anterior and inferior sites of infarct. Table 5.16 shows the relationship between infarct site

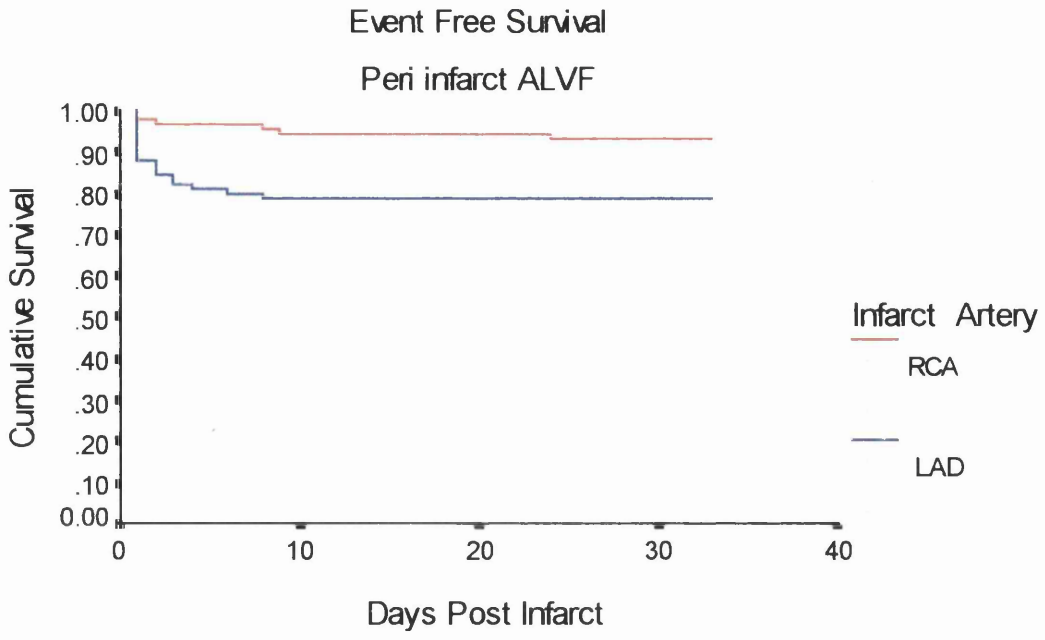

Figure 5.7 Infarct Related Artery and Peri-Infarct Acute Left Ventricular Failure

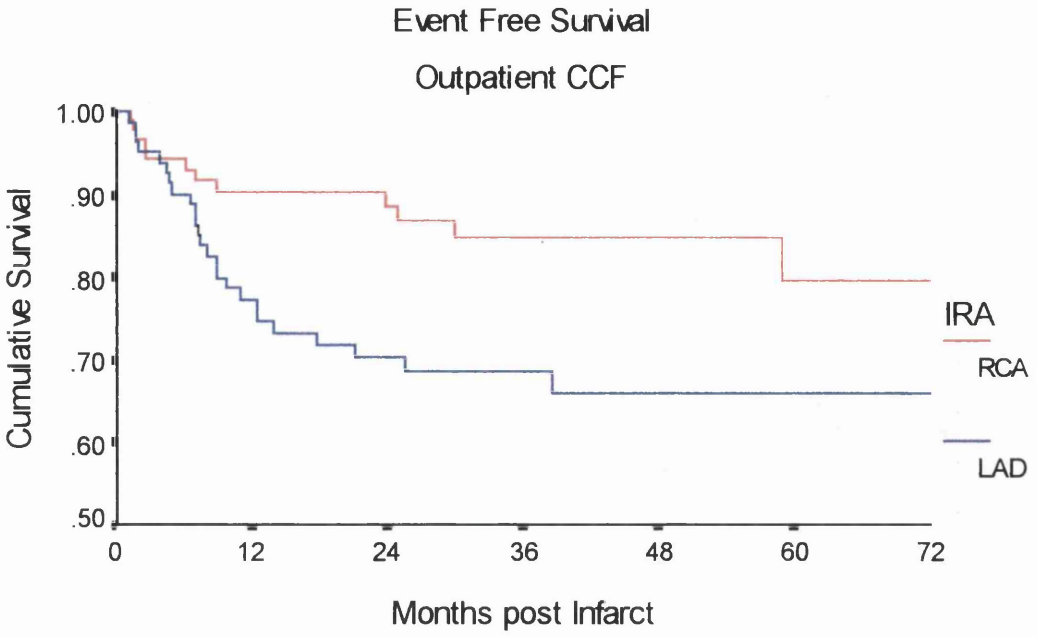

Figure 5.8 Infarct Related Artery and Congestive Heart Failure as an Outpatient

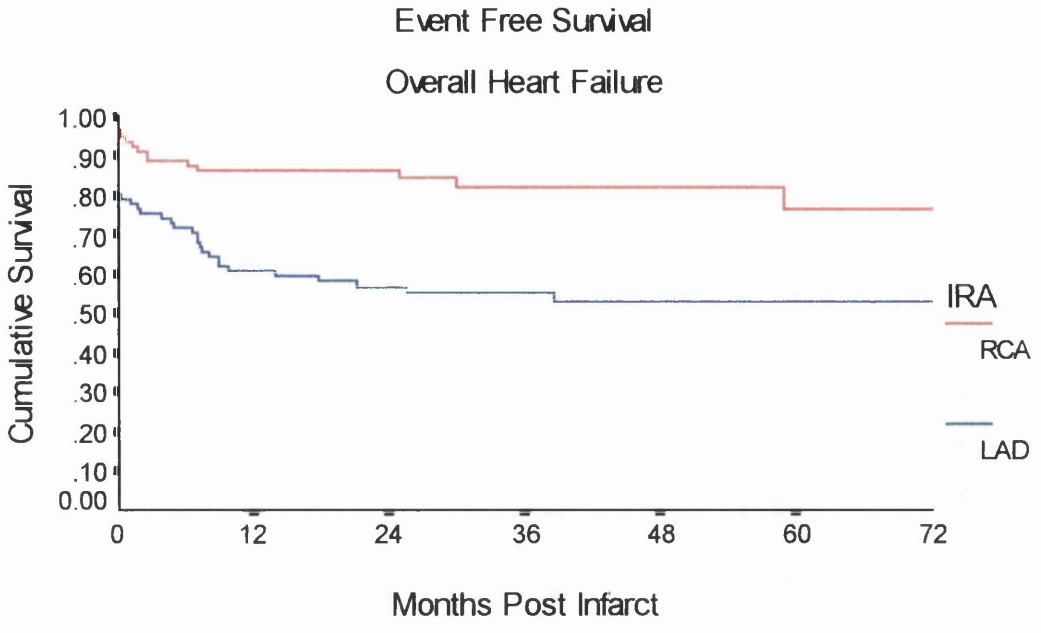

Figure 5.9 Infarct Related Artery and Heart Failure Overall

and infarct related artery. 87% of inferior and 96% of anterior infarcts could be attributed the RCA and LAD arteries respectively. This definition of infarct site allows inclusion of CX artery in the analysis as 12 inferior infarcts had CX occlusions as infarct related artery.

	IRA	Total Patients	Total Events	%	P Value
Ischemic pain	LAD	91	10	11	
	RCA	94	9	9	0.752
Acute LVF	LAD	91	19	20	
	RCA	94	6	6	**0.003**
All Cardiac Events	LAD	91	16	17	
	RCA	94	14	15	0.641

Table 5.12 Infarct Related Artery and In Hospital Cardiac Events

	IRA	Total Patients	Total Events	%	P Value
Angina	LAD	91	33	37	
	RCA	94	77	82	0.505
Heart Failure	LAD	91	26	28	
	RCA	94	12	13	**0.014**
All Cardiac Events	LAD	91	36	39	
	RCA	94	33	35	0.956

Table 5.13 Infarct Related Artery and Outpatient Cardiac Events

	IRA	Total Patients	Total Events	%	P Value
Mortality	LAD	91	9	10	
	RCA	94	5	5	0.136
Heart Failure	LAD	91	40	44	
	RCA	94	15	16	**0.001**
All cardiac Events	LAD	91	46	52	
	RCA	94	37	40	0.456

Table 5.14 Infarct Related Artery an overall Cardiac Events

Site of Infarct	n =	%
Anterior	85	44
Inferior	103	53.5
lateral	5	2.5

Table 5.15 Site of Infarct

Site of Infarct	LAD	RCA	CX
Anterior	78	1	1
Inferior	1	87	12
lateral	2	0	2

Table 5.16 Infarct site and infarct related artery

Table 5.17 shows the relationship between infarct site and exercise variables using Chi squared analysis. Patients with anterior compared to inferior infarcts had a reduced exercise capacity failing to achieve the median work load of 5.8 mets (63% v 39%,$p<0.05$) and greater incidence of inadequate systolic BP response during the exercise test (77% v 50%,$p<0.05$). This is illustrated in fig 5.10. 50% of patients with anterior myocardial infarction had ST segment elevation in the infarct site compared to 10% with inferior infarcts ($p< 0.001$). Similarly 54% of patients with anterior compared to 31% of patients with inferior infarcts had T wave normalisation in the infarct site during exercise testing ($p<0.05$). However ST segment depression occurred more often in patients with inferior compared to anterior infarcts (47% v 27%,$p< 0.05$). ST -T changes during exercise testing and infarct related artery are illustrated in fig 5.11.

Exercise Variables n=(%Total)	Anterior n=(%Total)	Inferior n=(%Total)	χ^2	P Value
Exercise Time < 540 sec n = 65 (44)	35 (53)	30 (37)	3.771	NS
Workload < 5.8 mets n = 66 (49)	38 (63)	28 (39)	7.237	**<0.05**
Δ Double Product < 8500 n = 21 (45)	11 (39)	10 (55)	1.169	NS
Δ Systolic BP < 30 mmHg n = 28 (60)	14 (77)	14 (50)	3.549	**< 0.05**
Symptomatic n = 69 (47)	34 (53)	35 (43)	1.007	NS
Angina n = 18 (12)	8 (12)	10 (12)	0.002	NS
ST Depression n = 56 (38)	18 (27)	38 (47)	5.949	**< 0.05**
ST Elevation n = 41 (28)	33 (50)	8 (10)	28.651	**< 0.001**
T Normalisation n = 61 (41)	36 (54)	25 (31)	8.401	**< 0.05**

Table 5.17 Infarct Site and Exercise Variables

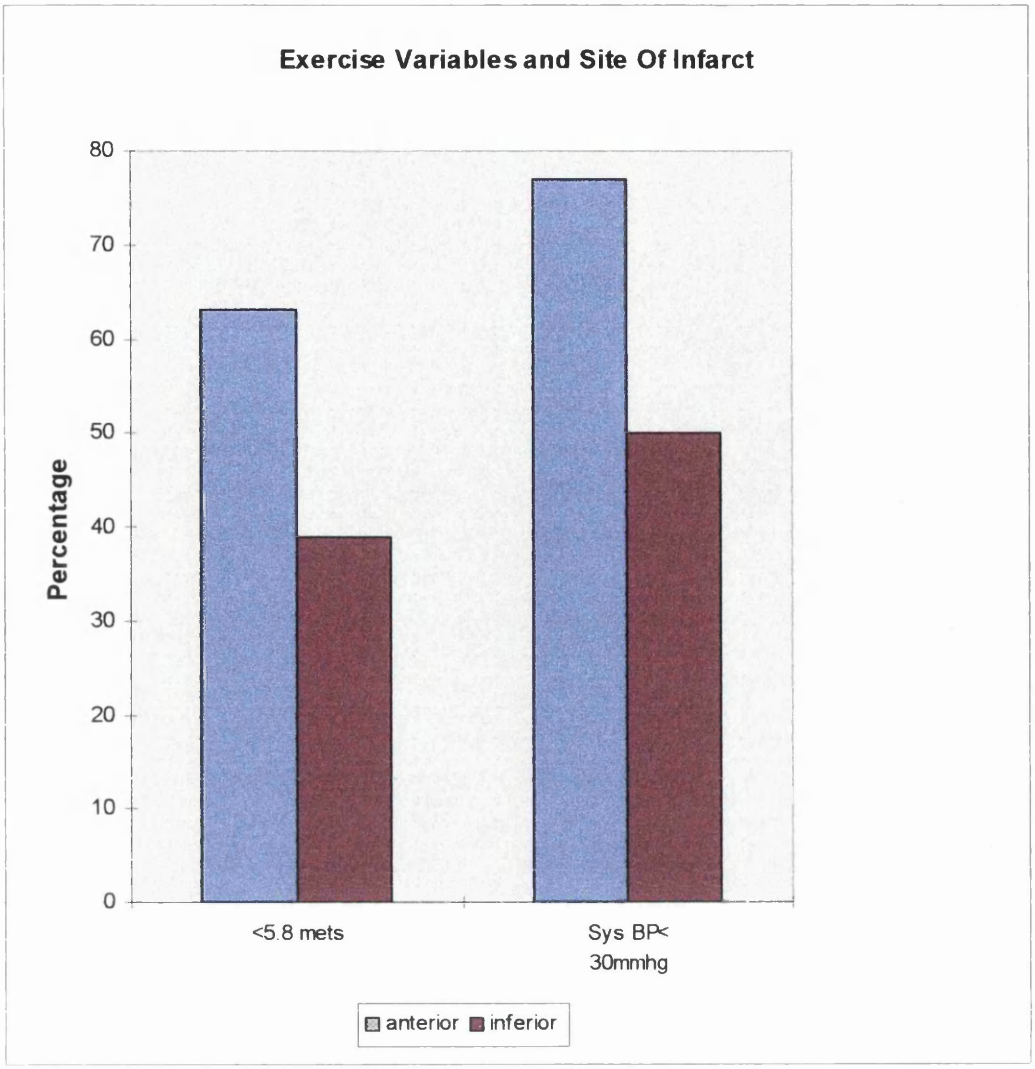

Figure 5.10 Site of Infarct and Exercise Variables

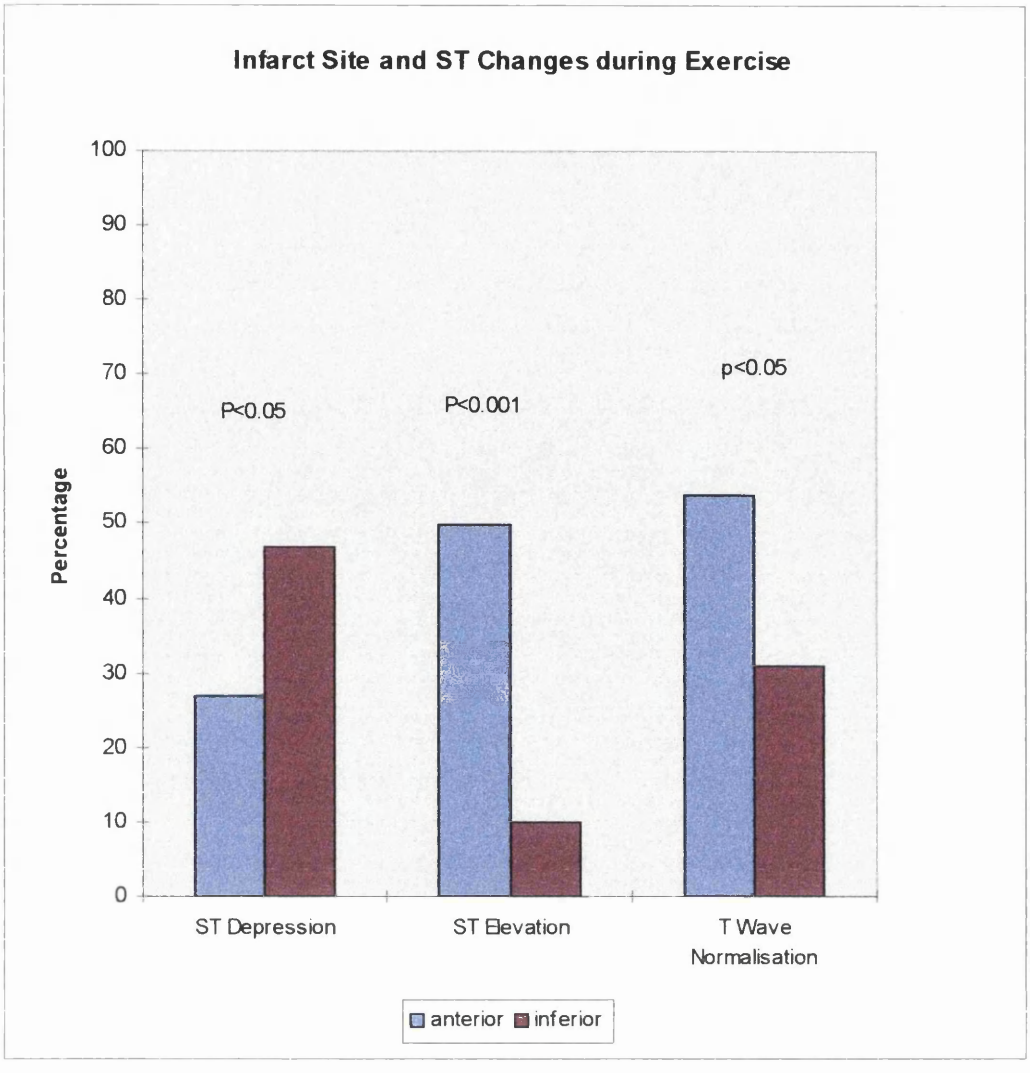

Figure 5.11 Infarct Site and ST Changes during Exercise

	Infarct Site	Total Patients	Total Events	%	P Value
Ischemic pain	Inferior	103	11	11	
	Anterior	90	7	8	0.454
Acute LVF	Inferior	103	7	7	
	Anterior	90	14	16	**0.051**
All Cardiac Events	Inferior	103	17	16	
	Anterior	90	11	12	0.395

Table 5.18 Infarct Site and in Hospital Cardiac Events

	Infarct Site	Total Patients	Total Events	%	P Value
Angina	Inferior	103	43	42	
	Anterior	90	33	37	0.299
Heart Failure	Inferior	103	16	16	
	Anterior	90	27	30	**0.055**
All Cardiac Events	Inferior	103	38	37	
	Anterior	90	38	43	0.845

Table 5.19 Infarct Site and Outpatient Cardiac Events

	Infarct Site	Total Patients	Total Events	%	P Value
Mortality	Inferior	103	9	9	
	Anterior	90	7	7	0.948
Heart Failure	Inferior	103	19	18	
	Anterior	90	36	40	**0.002**
All cardiac Events	Inferior	103	43	42	
	Anterior	90	44	51	0.980

Table 5.20 Infarct Site and Overall Cardiac Events

As shown in tables 5.18, 5.19 and 5.20 patients with anterior infarcts compared to inferior infarcts have a significantly increased incidence of peri infarct Acute LVF (16% v 7% p=0.051),heart failure as an outpatient, (27% v 16% p=0.055) and heart failure overall(36% v 19% p=0.002) . The corresponding Kaplan Meier curves are shown in fig 5.12, 5.13 and 5.14.

5.1.5 Reciprocal Depression

Patients with reciprocal depression (RD) on the admission ECG were identified. The effects of reciprocal depression on the results of exercise testing by Chi squared analysis are shown in table 5.21. The effect of reciprocal depression on clinical outcome is shown in tables 5.22 5.23 and 5.24. Patients with reciprocal depression have a significantly greater incidence of ST segment depression during exercise testing (51% v 21%, $p<0.01$) but a reduced incidence of ST segment elevation (22% v 35%,$p<0.05$)during exercise testing compared to those without reciprocal depression on the original admission ECG. This is illustrated in fig 5.15. 22 % of Patients with cardiac pain post infarct had reciprocal depression on the admission ECG compared to 9% of patients without, p=0.021. The incidence of Peri infarct acute left ventricular failure was significantly greater in patients with reciprocal depression (17% v 6%,p=0.027). This is illustrated in Fig 5.16. There was no difference in frequency of events as an outpatient or overall with reciprocal depression on the admission ECG.

5.1.6 Time to treatment

Time from onset of symptoms of myocardial infarction to administration of thrombolysis was divided into 3 time intervals 0-2hrs, 2-4hrs and 4-6 hrs. The distribution of patients within each time interval is shown in table 5.25. 68% of patients were treated within 4hrs of onset of symptoms. The effect of time to treatment on exercise variables by Chi squared analysis is shown in table 5.26. This is illustrated in fig 5.17. The effect of time to treatment on clinical outcome is shown in tables 5.27, 5.28 and 5.29.

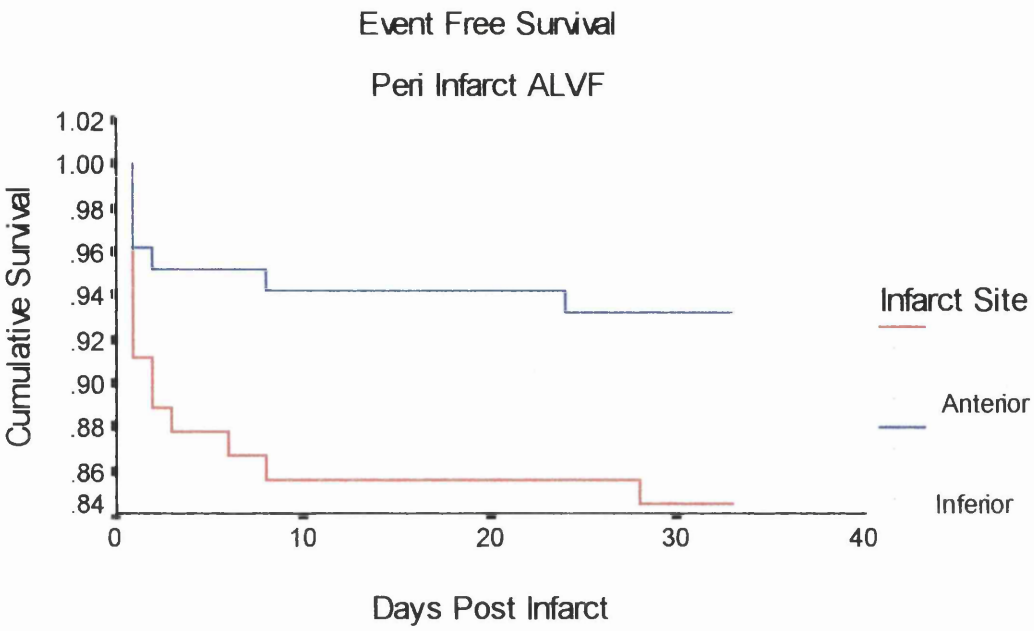

Figure 5.12 Infarct Site and Acute Peri-Infarct Left Ventricular Failure

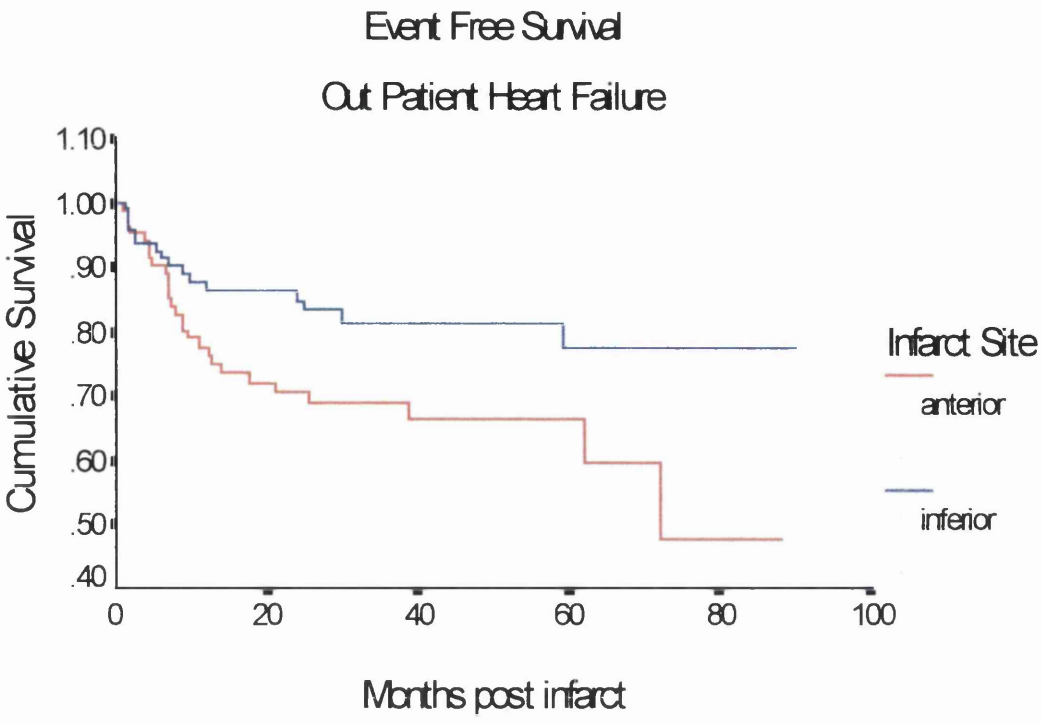

Figure 5.13 Infarct Site and Congestive Cardiac Failure as an Outpatient

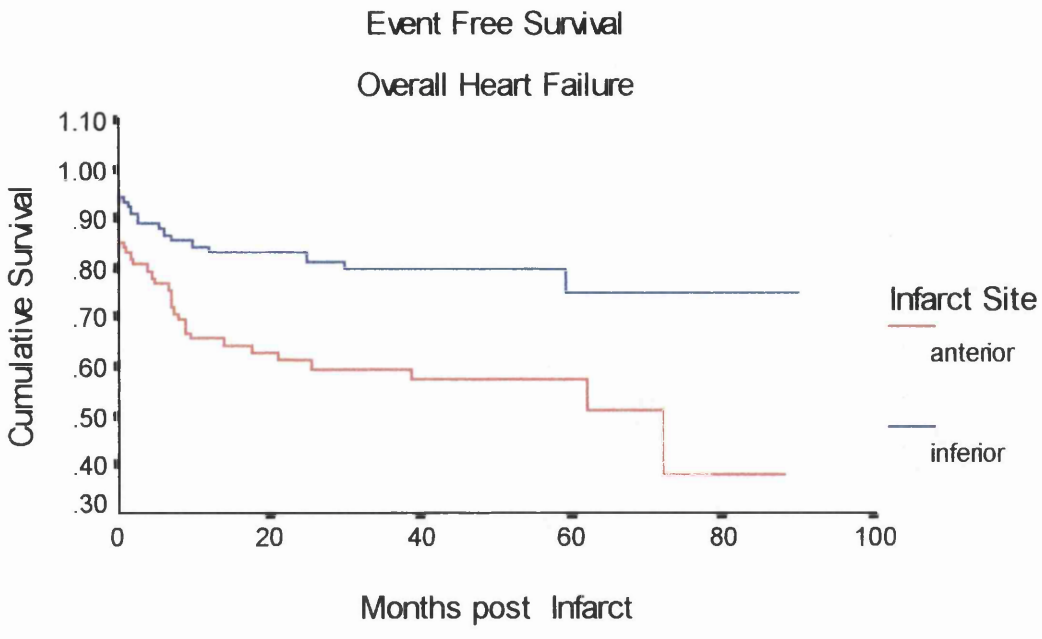

Figure 5.14 Infarct Site and Heart Failure Overall

Exercise Variables	No RD	RD	χ^2	P Value
Exercise Time < 540 sec n = 65 (44)	26 (41)	39 (46)	0.388	NS
Workload < 5.8 mets n = 66 (50)	30 (52)	36 (48)	0.181	NS
Δ Double Product < 8500 n = 21 (46)	8 (44)	13(46)	0.017	NS
Δ Systolic BP < 30 mmHg n = 28 (60)	10(56)	18(64)	0.351	NS
Symptomatic n = 69 (47)	33(52)	36(43)	1.311	NS
Angina n = 18 (12)	7(11)	11(13)	0.132	NS
ST Depression n = 56 (38)	13(21)	43(51)	14.252	**P< 0.01**
ST Elevation n = 41 (28)	22(35)	18(22)	3.896	**P<0.05**
T Normalisation n = 61 (41)	29(46)	32(38)	0.934	NS

Table 5.21 Reciprocal Depression and Exercise Variables

	RD	Total Patients	Total Events	%	P Value
Ischemic pain	No RD	79	7	9	
	RD	133	29	22	**0.021**
Acute LVF	No RD	79	5	6	
	RD	133	23	17	**0.027**
All Cardiac Events	No RD	79	7	16	
	RD	133	29	12	0.395

Table 5.22 Reciprocal Depression and in Hospital Cardiac Events

	RD	Total Patients	Total Events	%	P Value
Angina	No RD	79	28	36	
	RD	133	50	38	0.676
Heart Failure	No RD	79	19	24	
	RD	133	24	18	0.419
All Cardiac Events	No RD	79	28	35	
	RD	133	51	39	0.972

Table 5.23 Reciprocal Depression and Outpatient Cardiac Events

	RD	Total Patients	Total Events	%	P Value
Mortality	No RD	79	8	10	
	RD	133	15	11	0.684
Heart Failure	No RD	79	22	28	
	RD	133	40	30	0.219
All Cardiac Events	No RD	79	32	40	
	RD	133	64	48	0.166

Table 5.24 Reciprocal Depression and Overall Cardiac Events

	No of Patients	%
0-2 hrs	27	1 3
2-4 hrs	117	5 5
4-6 hrs	68	3 2

Table 5.25 Time to Treatment Groups

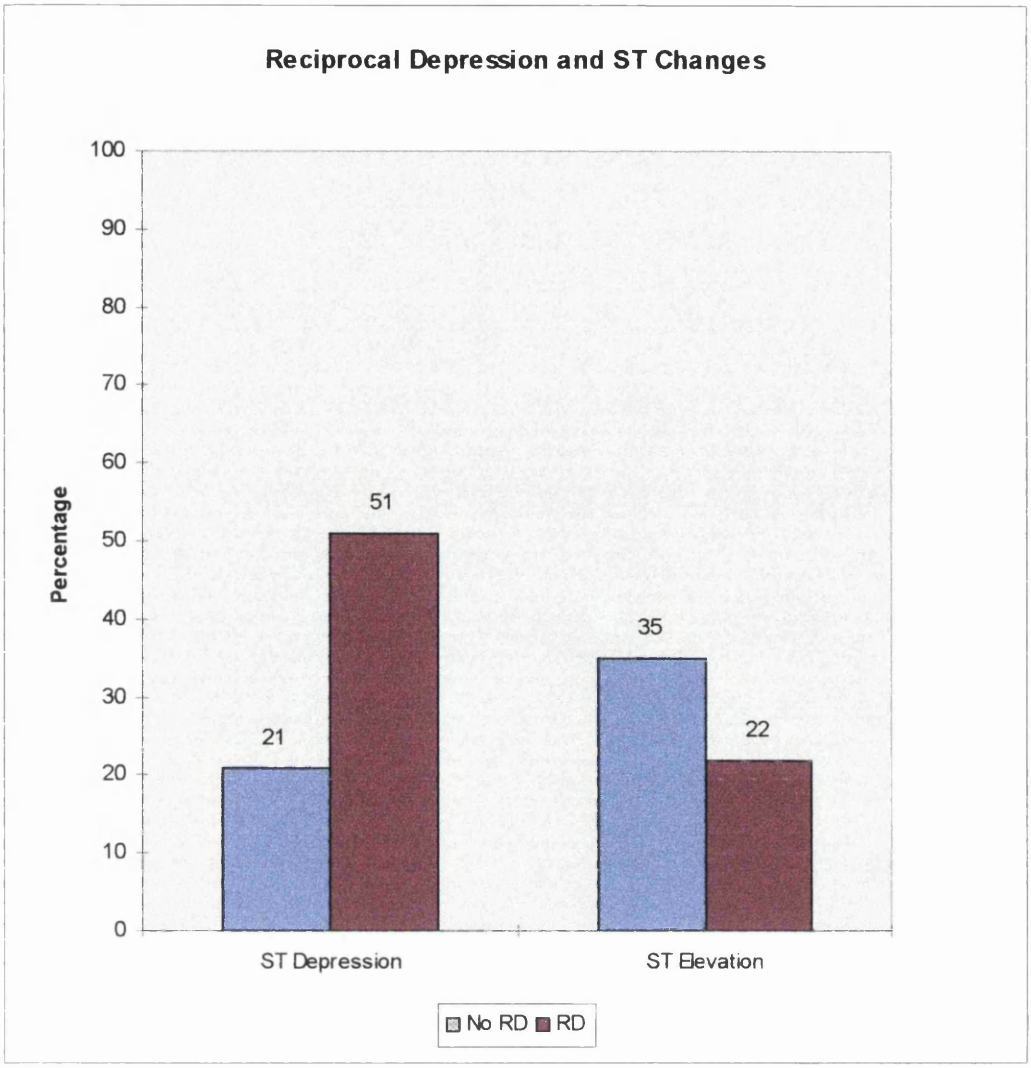

Figure 5.15 Reciprocal Changes and ST Segment changes during Exercise

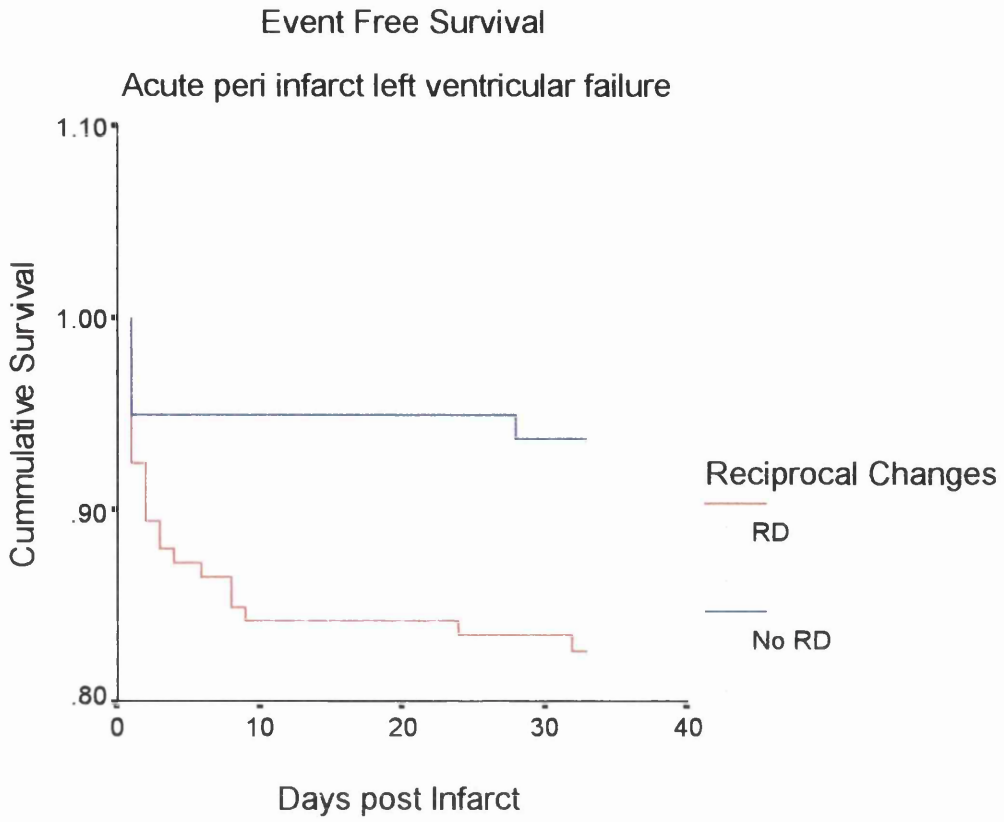

Figure 5.16 Acute peri infarct left ventricular failure and Reciprocal Changes

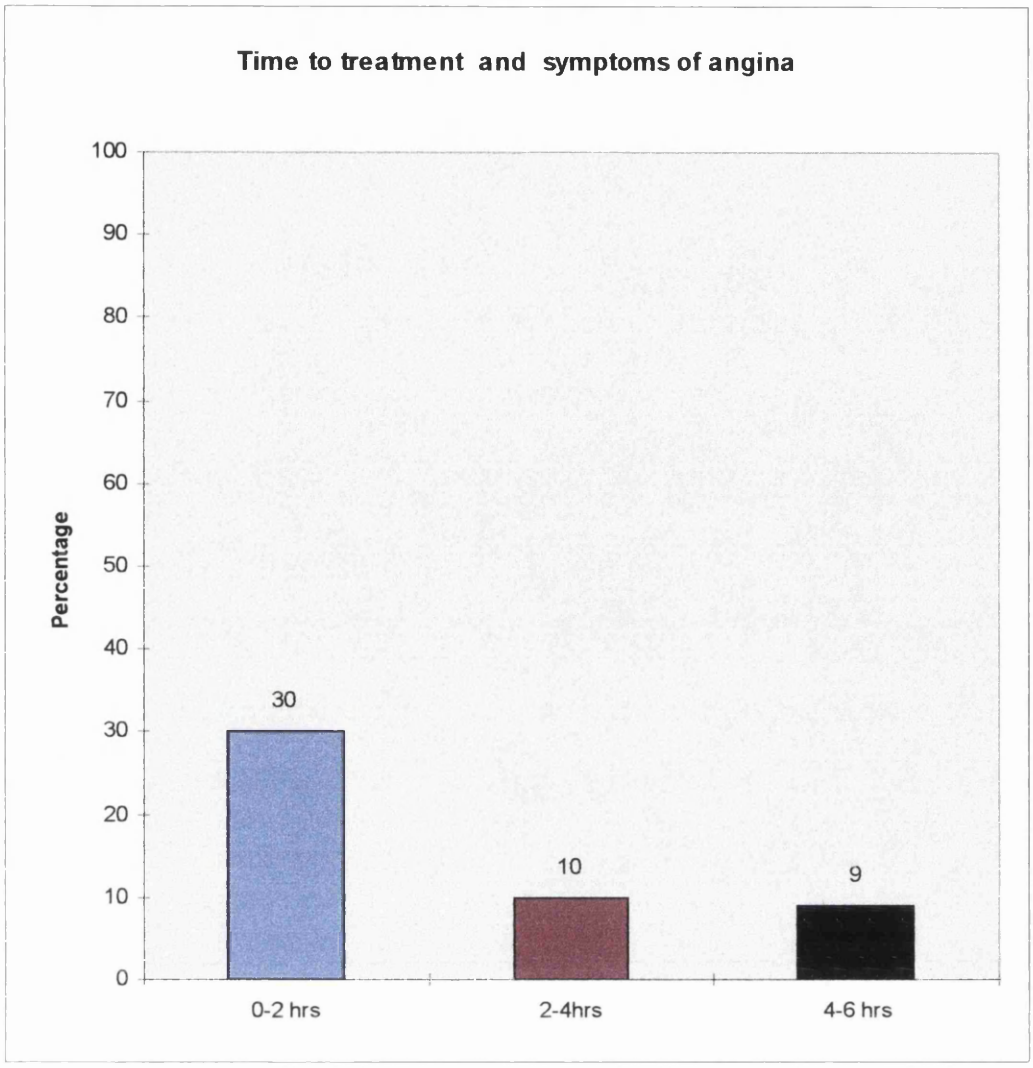

Figure 5.17 Time to treatment and Angina during Exercise Testing

	Time to Therapy				
Exercise Variables n=(%Total)	**0-2 hrs** n=(%Total)	**2-4 hrs** n=(%Total)	**4-6 hrs** n=(%Total)	**X 2**	**P Value**
Exercise Time< 540 sec n = 69 (44)	9(45)	34(37)	26(56)	4.341	NS
Workload < 5.8 mets n = 71 (50)	9(50)	39(46)	23(58)	1.329	NS
Δ Double Product < 500 n = 23 (48)	5(8)	13(46)	7(58)	0.894	NS
Δ Systolic BP< 30 mmHg n = 30 (62)	6(75)	17(60)	7(58)	0.660	NS
Symptomatic n = 86 (55)	11(55)	49(54)	26(56)	0.053	NS
Angina n = 19 (12)	6 (30)	9(10)	4 (9)	6.860	**P<0.05**
ST Depression n = 60 (38)	10(50)	29(31)	12(25)	3.386	NS
ST Elevation n = 42 (27)	4 (20)	25(28)	13(28)	0.562	NS
T Normalisation n = 65 (42)	10(50)	41(46)	14(30)	3.519	NS

Table 5.26 Time to Treatment and Exercise Variables

	Time to Therapy	Total Patients	Total Events	%	P Value
Ischemic pain	0-2 hrs	27	4	15	
	2-4 hrs	117	13	11	
	4-6 hrs	68	4	6	0.324
Acute LVF	0-2 hrs	27	16	15	
	2-4 hrs	117	8	14	
	4-6 hrs	68	6	1	0.909
All Cardiac Events	0-2 hrs	27	6	22	
	2-4 hrs	117	22	19	
	4-6 hrs	68	8	1	0.303

Table 5.27 Time to Treatment and in Hospital Cardiac Events

	Time To Therapy	Total Patients	Total Events	%	P Value
Angina	0-2 hrs	27	12	44	
	2-4 hrs	117	51	28	
	4-6 hrs	68	16	24	0.059
Heart Failure	0-2 hrs	27	6	22	
	2-4 hrs	117	22	19	
	4-6 hrs	68	15	23	0.727
All Cardiac Events	0-2 hrs	27	15	56	
	2-4 hrs	117	38	33	
	4-6 hrs	68	22	33	0.116

Table 5.28 Time to treatment and Outpatient Cardiac Events

	Time to Therapy	Total Patients	Total Events	%	P Value
Mortality	0-2 hrs	27	6	22	
	2-4 hrs	117	10	9	
	4-6 hrs	68	7	10	0.530
Heart Failure	0-2 hrs	27	8	29	
	2-4 hrs	117	34	30	
	4-6 hrs	68	20	30	0.980
All Cardiac Events	0-2 hrs	27	16	59	
	2-4 hrs	117	53	46	
	4-6 hrs	68	27	40	0.465

Table 5.29 Time to Treatment and Overall Cardiac Events

As shown, the development of angina during exercise testing was related to early thrombolysis. 30% of patients who received treatment within 2 hrs experiencing symptoms during exercise testing $p<0.05$. Patients treated with thrombolysis within 2 hrs of the onset of symptoms were more likely to develop angina during outpatient follow up, $p=0.058$. This is further illustrated by the multiple comparisons of time to therapy groups for angina during the follow up period. Table 5.30 shows the p values for inter group comparisons

Time to therapy	0-2 hrs	2-4 hrs
2-4 hrs	0.577	
4-6 hrs	**0.051**	**0.033**

Table 5.30 Multiple comparisons (p values) of Time to Therapy groups and Angina as an outpatient.

The effect of time to treatment on clinical outcome showed a trend towards increased frequency of all cardiac events as an outpatient with early thrombolysis, $p=0.116$. Multiple comparisons (p Values) of individual time to therapy groups show significant differences between thrombolysis at 0-2 hrs compared to 2-4 hrs ($p=0.049$)) as shown in table 5.31.

Time to therapy	0-2 hrs	2-4 hrs
2-4 hrs	**0.049**	
4-6 hrs	0.097	0.745

Table 5.31 Multiple comparisons (p values) of Time to Therapy and All Cardiac Events as an Outpatient

5.2 Exercise Variables In The Prediction Of Clinical Outcome

5.2.1 Exercise Capacity

The results of the exercise test were used to predict future cardiac events but not related retrospectively to results of in patient peri infarct data e.g. exercise capacity was not used as an independent variable to predict patency but patency was used to predict the results of exercise testing. 156 patients exercised for a mean of 543 $\pm$ 205 secs, range 64-1093 sec. The median exercise time was 540 secs. Table 5.32 shows the relationship between median exercise time and outpatient events. Patients were divided into 2 groups: those who failed to achieve the median exercise time (< 540 secs) and compared to those patients who achieved the median time or greater ($\geq$ 540 secs).

The average metabolic equivalents achieved by the patients was 5.9 $\pm$ 2.4 mets, range 2.3-12.9 mets. The median workload achieved was 5.8 mets. Table 5.33 shows the relationship between median mets and outpatient events. As shown there was no relationship between exercise capacity measured as total exercise time or metabolic equivalents time and cardiac events during outpatient follow up.

	Time	Total Patients	Total Events	%	P Value
Angina	<540 sec	67	24	36	
	≥540 sec	87	39	45	0.287
Heart Failure	<540 sec	69	10	14	
	≥540 sec	87	20	23	0.281
All Cardiac Events	<540 sec	69	24	36	
	≥540 sec	87	35	40	0.763
Mortality	>540 sec	69	4	6	
	≥540 sec	87	3	3	0.721

Table 5.32 Exercise Capacity (in Secs) and Outpatient Cardiac Events

	Mets	Total Patients	Total Events	%	P Value
Angina	<5.8 mets	70	28	40	
	>5.8 mets	71	30	43	0.836
Heart Failure	<5.8 mets	71	13	18	
	>5.8 mets	71	15	21	0.826
All Cardiac Events	<5.8 mets	71	21	29	
	>5.8 mets	71	28	39	0.741
Mortality	>5.8 mets	71	2	3	
	>5.8 mets	71	3	4	0.978

Table 5.33 Exercise Capacity (in Mets) and Outpatient Cardiac Events

5.2.2 Systolic Blood Pressure

The mean change in systolic BP was 20 ± 15.7 mmHg, range -12 to 70 mmHg. The failure to increase systolic blood pressure by 30 mmHg, shown by previous studies to be a poor prognostic indicator, was chosen to identify those patients who had an adequate systolic Blood Pressure response (≥ 30 mmHg) to exercise. This was used to predict future outpatient cardiac events. As shown in Table 5.34 Systolic blood pressure response during exercise testing was not useful in identifying patients at high risk of future cardiac events.

	BP	Total Patients	Total Events	%	P Value
Angina	<30 mmHg	30	11	37	
	≥30 mmHg	18	7	39	0.392
Heart Failure	<30 mmHg	30	7	23	
	≥30 mmHg	18	3	17	0.173
All Cardiac Events	<30 mmHg	30	11	37	
	≥30 mmHg	18	7	39	0.465
Mortality	>30 mmHg	30	3	10	
	≥30 mmHg	18	1	5	0.562

Table 5.34 Systolic Blood Pressure Rise and Outpatient Cardiac Events

5.2.3 Rate Pressure Product

The mean change in rate pressure product (RPP) during exercise was 8983 ± 3255, range 3248-19970. The median change in rate pressure product was 5800. Table 5.35 shows that change in rate pressure product fails to predict outpatient events in this study during follow up.

	RPP	Total Patients	Total Events	%	P Value
Angina	<5800	23	9	33	
	≥5800	25	9	36	0.603
Heart Failure	<5800	23	5	22	
	≥5800	25	5	20	0.927
All Cardiac Events	<5800	23	9	33	
	≥5800	25	9	36	0.627
Mortality	>5800	23	2	9	
	≥5800	25	2	8	0.818

Table 5.35 Change in Double Product and Outpatient Cardiac Events

5.2.4 ST-T Changes During Exercise

5.2.4.1 ST Segment Depression

ST segment depression of ≥ 1 mm, 80 m.sec after J point occurred in 60 (38%) of 156 patients undergoing exercise testing. The relationship between ST segment depression and cardiac events during follow up is shown in Table 5.36. ST segment depression did not predict future cardiac events as an outpatient. The infarct site was defined by ECG on admission, in 150 patients who were subsequently exercised prior to discharge. Of the 60 patients with ST depression it occurred in the non-infarct site in 52(87%) patients compared to 6(13%) patients in the site of the original infarct. 2 patients (3%) had ST depression in both infarct and non infarct sites. Therefore ST segment depression occurs predominantly in the non infarct site, 0.001, by Chi squared analysis. This is illustrated in figure 5.18.

	STD	Total Patients	Total Events	%	P Value
Angina	No STD	94	37	39	
	STD	60	26	43	0.108
Heart Failure	No STD	96	19	20	
	STD	60	11	18	0.764
All Cardiac Events	No STD	96	40	42	
	STD	60	19	48	0.721
Mortality	No STD	96	5	5	
	STD	60	2	3	0.655

Table 5.36 ST Segment Depression and Outpatient Cardiac Events

A further analysis was made using ST depression of ≥ 2 mm as significant. There was no improvement in the ability to predict clinical events.

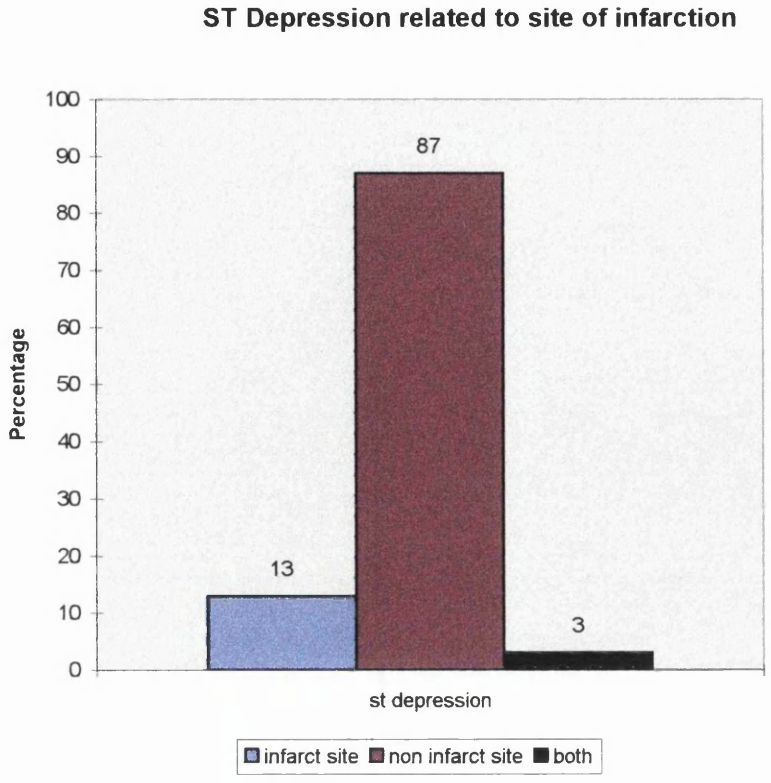

Figure 5.18 ST Segment Depression and Site of Infarct

5.2.4.2 ST Segment Elevation

ST elevation occurred in 42 (27%) of 156 patients exercised. As shown in table 5.37 and Fig 5.19 ST elevation occurred predominantly in the infarct site, as defined by admission ECG, compared to the non infarct site (83% v 17%,$p<0.001$):

Site of elevation	n	%
Infarct site	35	83
Non infarct site	7	17

Table 5.37 Site Of ST Segment Elevation

The relationship between ST elevation (STE) and outpatient cardiac events are shown in Table 5.38. ST segment elevation during exercise testing did not predict clinical outcome.

	ST ↑	Total Patients	Total Events	%	P Value
Angina	No STE	114	43	38	
	STE	42	20	48	0.393
Heart Failure	No STE	114	19	17	
	STE	42	11	26	0.637
All Cardiac Events	No STE	114	43	38	
	STE	42	16	38	0.721
Mortality	No STE	114	6	5	
	STE	42	1	2	0.565

Table 5.38 ST Segment Elevation and Outpatient Cardiac Events

5.2.4.3 T wave Normalisation

T wave normalisation (TE), defined as the return of a negative T wave on the pre test ECG to the isoelectric line or beyond during exercise testing, occurred in 65 (41%) of 156 patients exercised. This occurred exclusively in the site of infarction ($p<0.0001$). The relationship of T wave normalisation and outpatient cardiac events are summarised in Table

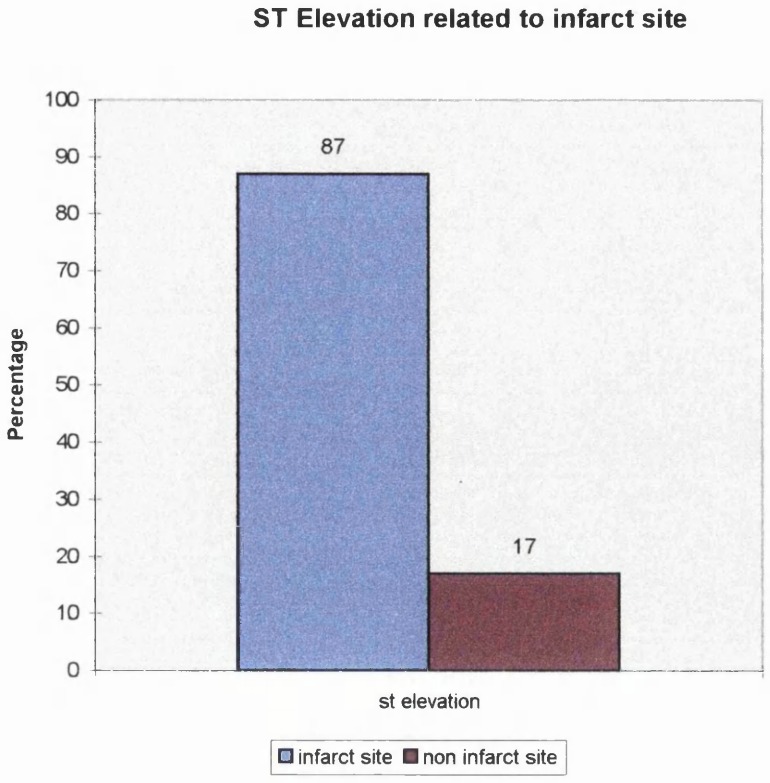

Figure 5.19 ST Segment Elevation and Site of Infarct

5.39. As shown T wave normalisation did not predict cardiac events although there was a trend for increased incidence of angina in those patients who had T wave normalisation.

	T ↑	Total Patients	Events	%	P Value
Angina	No TE	89	30	33	
	TE	65	33	50	0.097
Heart Failure	No TE	91	14	15	
	TE	65	13	20	0.265
All Cardiac Events	No TE	91	35	38	
	TE	65	24	37	0.996
Mortality	No TE	91	6	6	
	TE	65	1	2	0.252

Table 5.39 T Wave Normalisation and Outpatient Cardiac Events

5.2.4.4 ST Segment Depression at low workload

ST segment depression at a low workload was analysed to determine whether this improved the ability of ST depression predict future events. 25 patients (15%) with ST depression of ≥ 1 mm failed to achieve the median workload of 5.8 mets. The relationship between ST depression at low workload is shown in Table 5.40.

	STD	Total Patients	Total Events	%	P value
Angina	No STD	116	48	41	
	STD	25	10	40	0.960
Heart Failure	No STD	117	20	17	
	STD	25	8	32	0.764
All Cardiac Events	No STD	117	42	36	
	STD	25	7	28	0.267
Mortality	No STD	117	4	3	
	STD	25	1	4	0.647

Table 5.40 ST Segment Depression at a Low Workload and Outpatient Cardiac Events

Patients with ST segment depression at a low workload during the exercise test were no more likely to experience cardiac events compared to those without this abnormality.

5.3 Patients not undergoing exercise testing

The decision to perform predischarge exercise testing was at the discretion of the physician in charge of the patients care. The reason for not performing an Exercise test was not always recorded but this subgroup was compared to those undergoing exercise testing in the prediction of future cardiac events, as shown in Table 5.41. The 12 patients who died (10 from sudden cardiac deaths and 2 non cardiac death from CVA) during the inpatient period were not included in this analysis as they were not eligible to perform the exercise test and an event (in patient Mortality) cannot be ***predicted*** retrospectively. (26%) of patients did not undergo exercise testing. Patients failing to undergo exercise testing did not have an increased incidence of cardiac events. However when the deaths from non cardiac causes that occurred during outpatient follow up were included in the analysis patients who failed to undergo a predischarge exercise test had an increased mortality (18% v 5%, p=0.011). This is illustrated in Fig 5.22.

	ETT	Total Patients	Total Events	%	P value
Angina	No ETT	40	14	35	
	ETT	156	65	42	0.651
Heart Failure	No ETT	40	11	28	
	ETT	156	30	19	0.193
All Cardiac Events	No ETT	40	16	40	
	ETT	156	54	35	0.341
Outpatient Mortality	No ETT	40	3	7	
	ETT	156	6	4	0.366
All Deaths	No ETT	40	7	18	
	ETT	156	8	5	0.011

Table 5.41 No Exercise Testing and Cardiac Events

5.4 Symptoms During Exercise

5.4.1 All Symptoms during Exercise Testing

The exercise test was symptom limited .However if the patients reached an age predicted maximum heart rate ,developed significant arrhythmias or ST segment depression of ≥ 3 mm the test was terminated. Fig 5.20 shows the distribution of symptoms during exercise. Patients with any symptoms (SYMP) during the exercise test were compared with those who were asymptomatic. Then, patients with angina were compared to those patients with no symptoms of angina. 70 (45%) of patients were asymptomatic during exercise testing .Table 5.42 shows that combined symptoms during exercise testing did not predict outpatient cardiac events during follow up

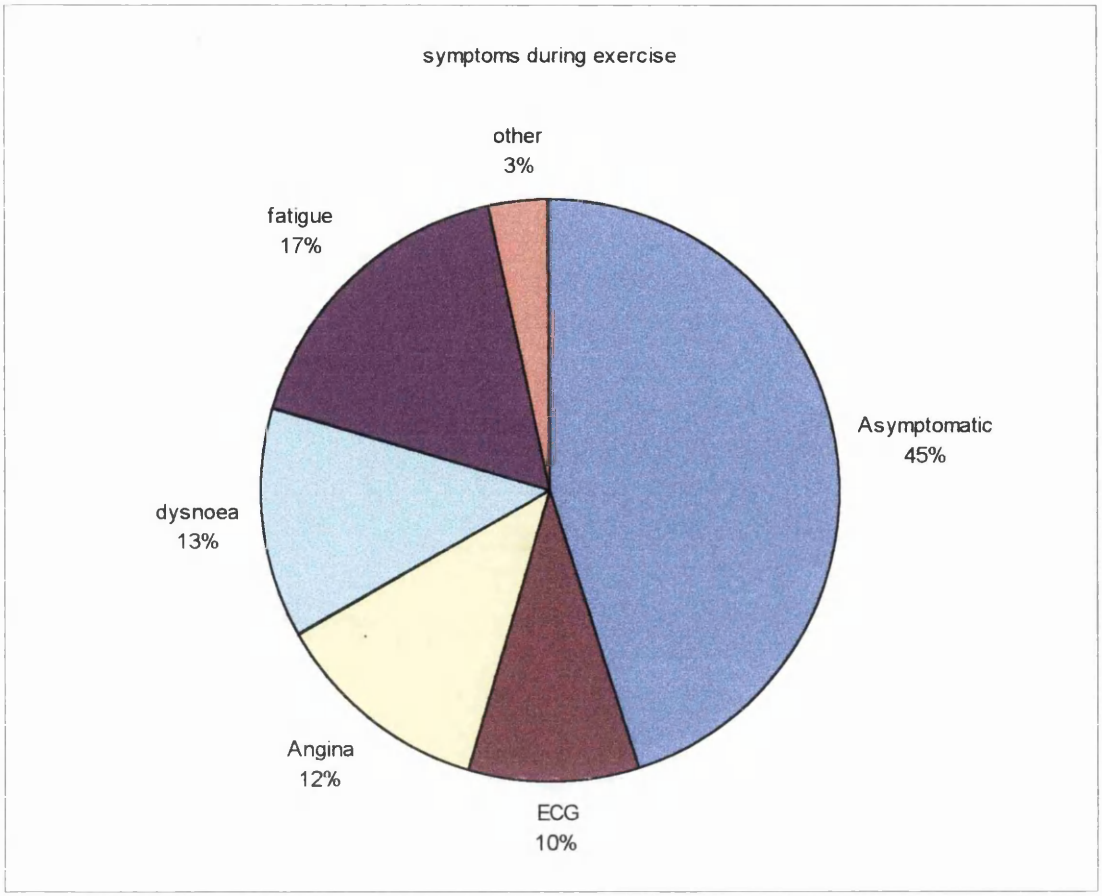

Figure 5.20 Symptoms during Exercise Testing

	Symptoms	Total Patients	Total Patients	%	P Value
Angina	No SYMP	68	24	35	
	SYMP	86	39	45	0.328
Heart Failure	No SYMP	70	11	16	
	SYMP	86	19	22	0.703
All Cardiac Events	No SYMP	70	24	34	
	SYMP	86	35	41	0.308
Mortality	No SYMP	70	4	6	
	SYMP	86	3	3	0.966

Table 5.42 All Symptoms Combined and Cardiac Events

5.4.2 Angina

19 patients (12%) developed angina (ANG) during the predischarge exercise test. The effects of angina on the cardiac events in the follow up period is shown in Table 5.43. This shows that 63% of patients who reported angina during the exercise test complained of angina as an outpatient compared to 37% of patients without angina (p=0.007). This is shown by event free survival analysis in Fig 5.21. The majority of patients develop angina within the first year of follow up.

	Angina	Total Patients	Total Events	%	P Value
Angina	No ANG	135	51	37	
	ANG	19	12	63	**0.007**
Heart Failure	No ANG	137	25	18	
	ANG	19	5	26	0.208
All Cardiac Events	No ANG	137	51	37	
	ANG	19	8	42	0.308
Outpatient Mortality	No ANG	137	7	5	
	ANG	19	0	0	0.382

Table 5.43 Angina during Exercise Testing and Outpatient Cardiac Events

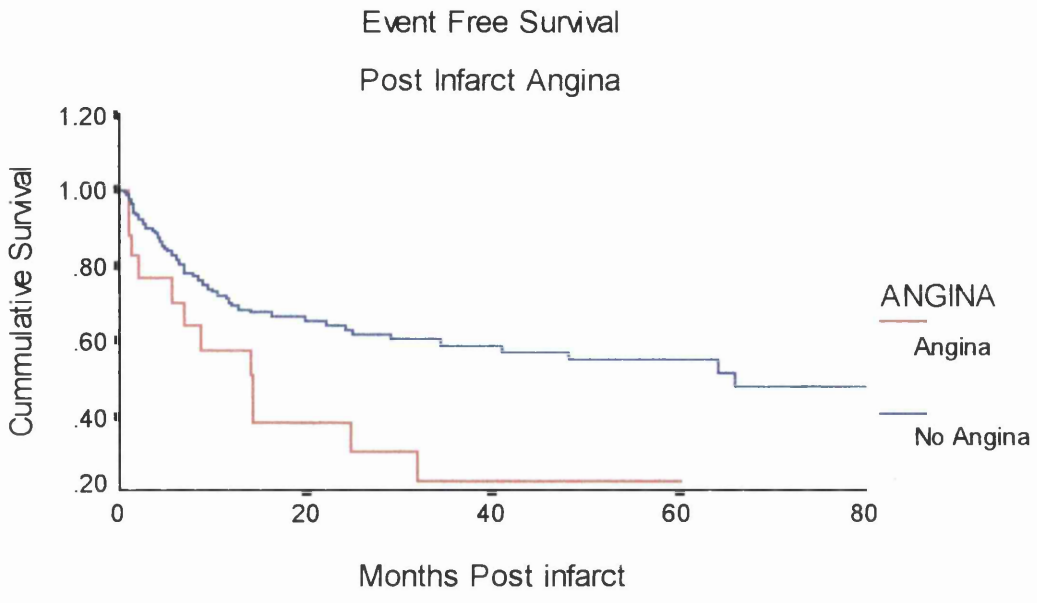

Figure 5.21 Event free Survival Analysis for Angina during Exercise and development of Post Infarct Angina

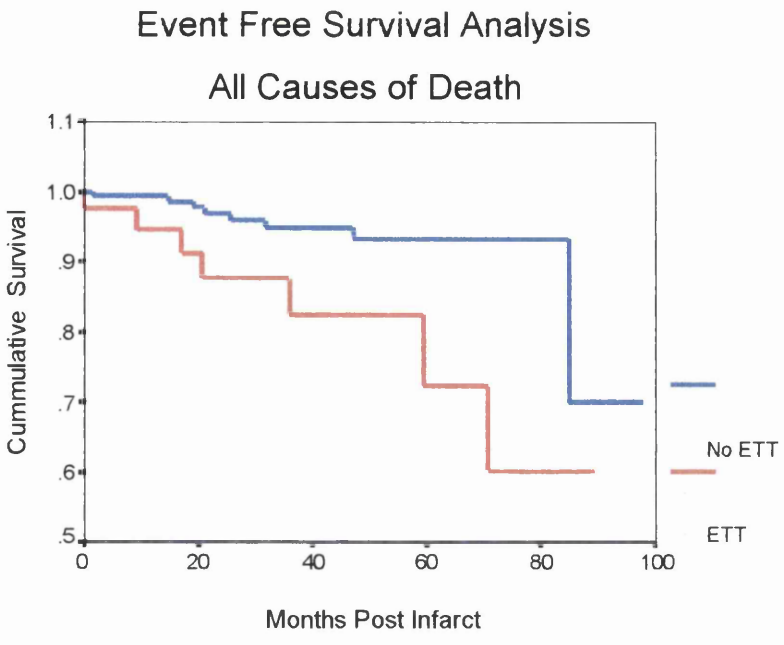

Figure 5.22 Event Free Survival Analysis of death from all Causes

6. THE EFFECT OF CORONARY PATENCY ON VARIABLES MEASURED DURING EXERCISE TESTING AND CLINICAL OUTCOME

Coronary artery patency of the infarct-related vessel was assessed by TIMI scoring of coronary angiograms performed at 90 mins and 24 hrs following thrombolysis. The TIMI Score was related to the results of Exercise Testing and used to predict clinical outcome.

6.1 TIMI Score at 90 mins

194 of 212 patients underwent angiographic assessment of patency at 90 mins post thrombolysis. Table 6.1 shows the distribution of the TIMI scores of the infarct related artery in these patients undergoing angiography at 90 mins. 31% of patients had persistent coronary occlusion TIMI score 0 at 90 min post thrombolysis, 36% had established full coronary patency, TIMI grade 3. This is illustrated in fig 6.1.

TIMI score 90 Mins	No. of Patients	%
0	60	31
1	14	7
2	51	26
3	69	36
Total	194	

Table 6.1 Distribution of TIMI Scores following angiography at 90 min

6.1.1 Symptoms reported during Exercise Testing

X^2 analysis was performed to determine whether there was any relationship between TIMI score at 90 mins and symptoms reported during exercise. As shown in table 6.2 TIMI score at 90 min did not affect the development of any symptoms, nor the development of angina during exercise testing. This is illustrated in and fig 6.2

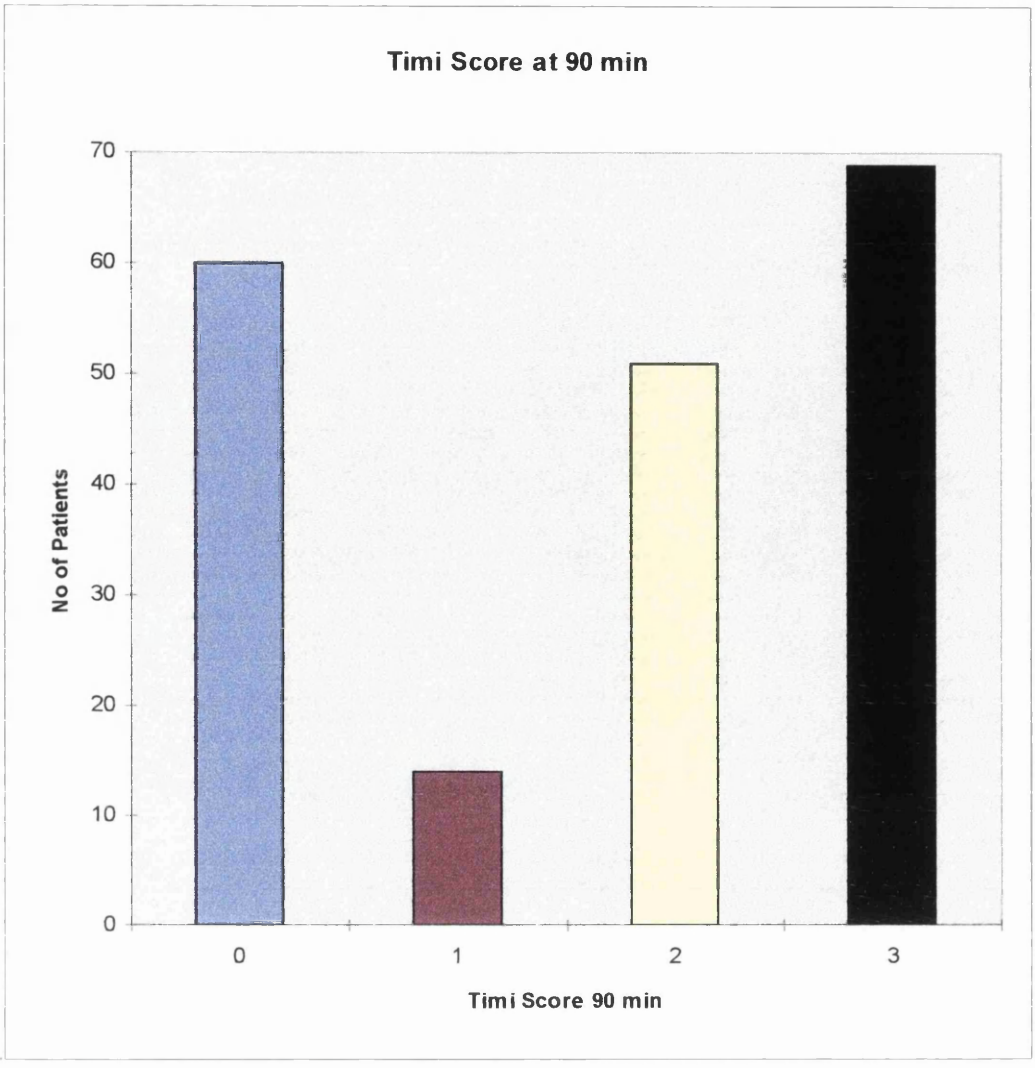

Figure 6.1 Distribution of TIMI Scores following angiography at 90 min.

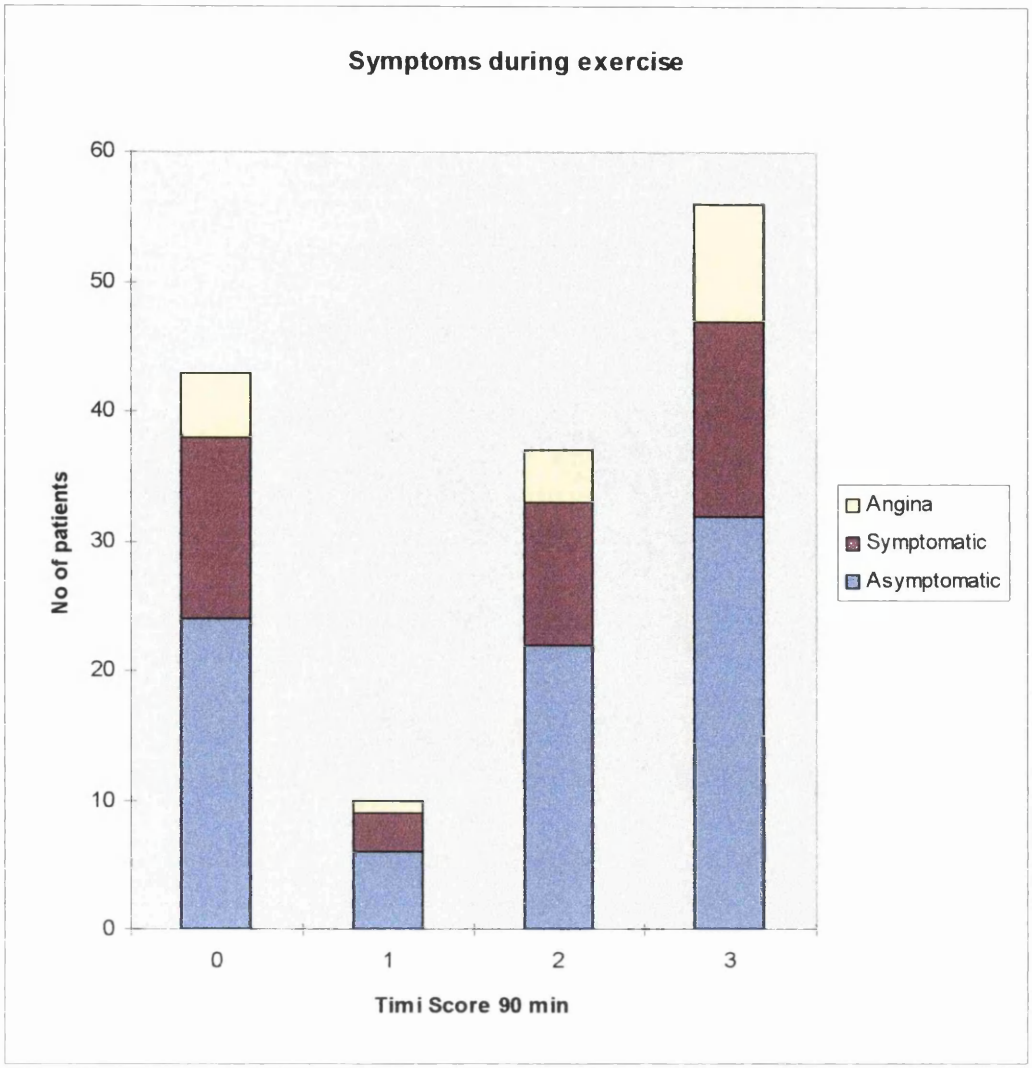

Figure 6.2 Symptoms during exercise testing related to the TIMI score folowing angiography at 90 mins

Symptoms	TIMI Score at 90 min			
	0	1	2	3
Asymptomatic	24	6	22	32
Symptomatic	19	4	15	26
(X^2 = 0.228, NS)				
No Angina	38	9	33	49
Angina	5	1	4	9
(X^2 = 0.636, NS)				

Table 6.2 Symptoms during exercise testing related to TIMI scoring of 90 min angiogram

6.1.2 ST-T Changes during Exercise testing

X^2 analysis was performed to determine whether there was any relationship between TIMI score at 90 mins and ST-T changes occurring during exercise testing. As shown in table 6.3 TIMI score at 90 min did not affect the development of ST depression, ST elevation or T wave normalisation during exercise testing. This is illustrated in fig 6.3.

ST-T Changes	TIMI Score at 90 min			
	0	1	2	3
ST Depression				
No ST↓	22	9	25	35
ST ↓	21	1	12	23
(X^2 = 5.978, NS)				
ST Elevation				
No ST↑	31	5	27	44
ST↑	12	5	9	14
(X^2 = 2.998, NS)				
T Wave Normalisation				
No T ↑	27	4	19	34
T ↑	16	6	18	24
(X^2 = 2.304, NS)				

Table 6.3 TIMI score at 90 mins and ST-T Changes during Exercise

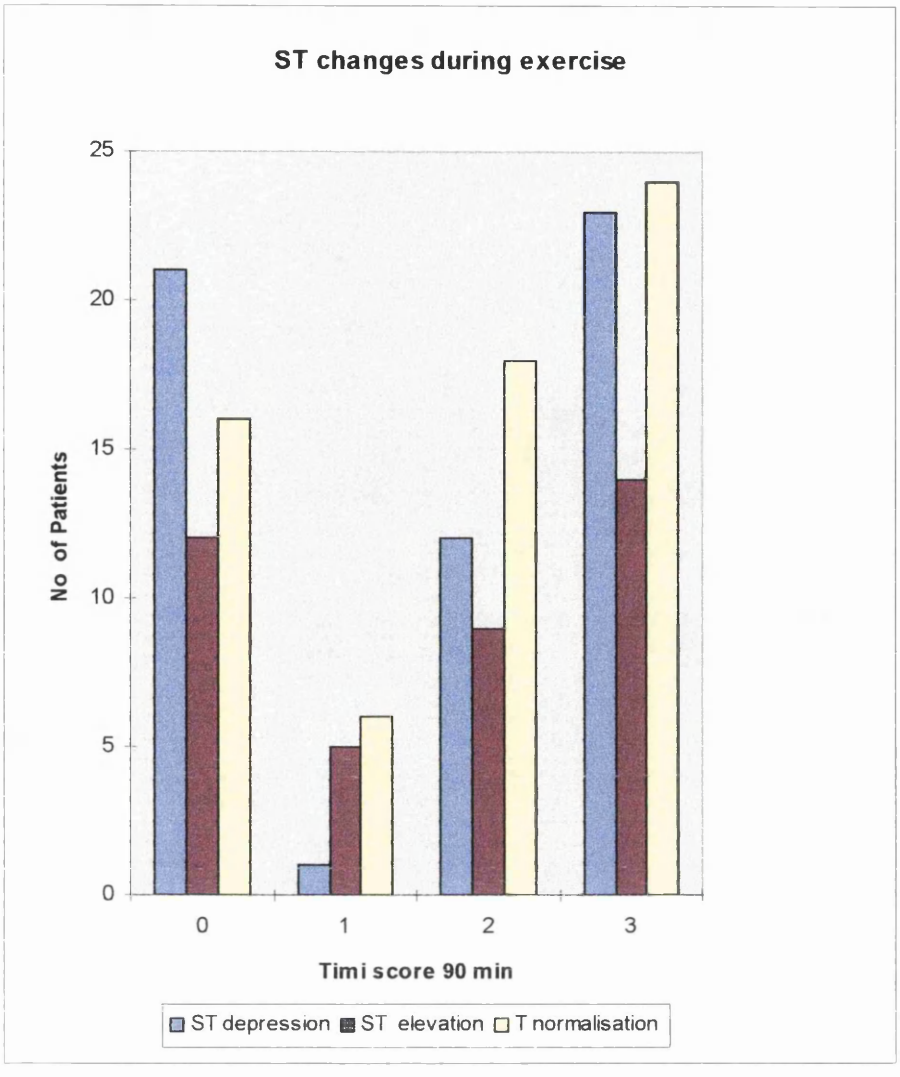

Figure 6.3 ST changes during exercise testing related to TIMI score of 90 min angiograms.

6.1.3 Functional Capacity

Analysis of variance showed no relationship between TIMI scoring at 90 mins and:

1. Total exercise time
2. Metabolic equivalents achieved during exercise
3. Failure to achieve median exercise capacity of 5.8 mets
4. Failure of Systolic blood pressure to increase by ≥ 30mmhg
5. Failure of rate pressure product to increase by ≥ 8500

6.2 TIMI Score at 24 hrs

Angiography was repeated at 24 hrs on 187 of the original 212 patients following thrombolysis and further assessed by TIMI scoring. The distribution of the TIMI score within the patients undergoing angiography at 24 hrs is shown below in Table 6.4. 83% of patients had patent infarct related vessels at 24 hrs (TIMI grade 2,3) with 58% full patency (TIMI Grade 3). However 12% of patients had no established coronary flow with TIMI Grade 0. This is illustrated in fig 6.4.

TIMI Score 24 hrs	No.of Patients	%
0	23	12
1	8	4
2	47	25
3	109	58
Total	187	

Table 6.4 Distribution of TIMI Scores following angiography at 24 hrs

6.2.1 Symptoms Reported During Exercise Testing

X^2 analysis was performed to determine whether there was any relationship between TIMI score at 24 hrs and symptoms reported during exercise or ST changes occurring during the pre-discharge exercise test. As shown below in table 6.5 although not statistically significant there was trend towards patients with TIMI score 1 and 2 being asymptomatic during exercise testing. All 6 patients (100%) with TIMI score 1 and 22 (66%) of the 36 patients with TIMI score 2 were asymptomatic. This is illustrated in Fig 6.5, TIMI score at 24 hrs did not affect the development of angina during exercise.

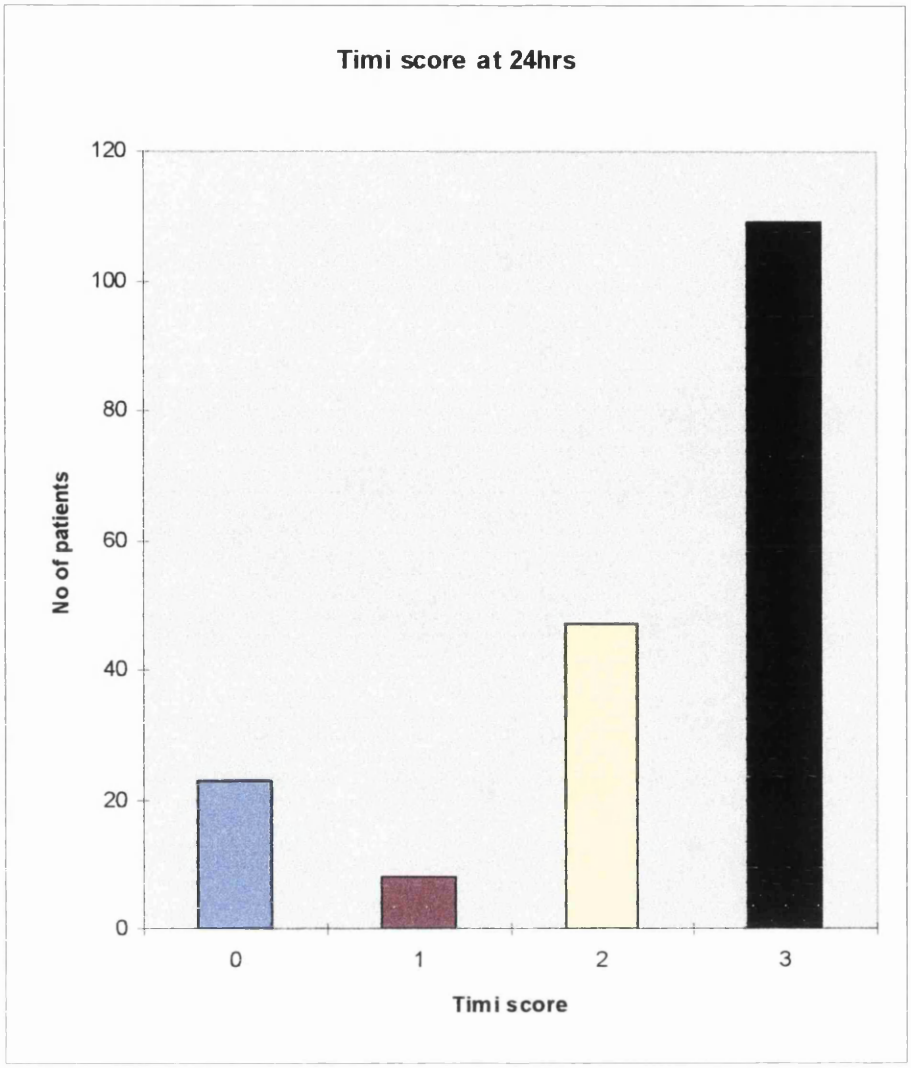

Figure 6.4 Distribution of TIMI Scores following angiography at 24 hrs.

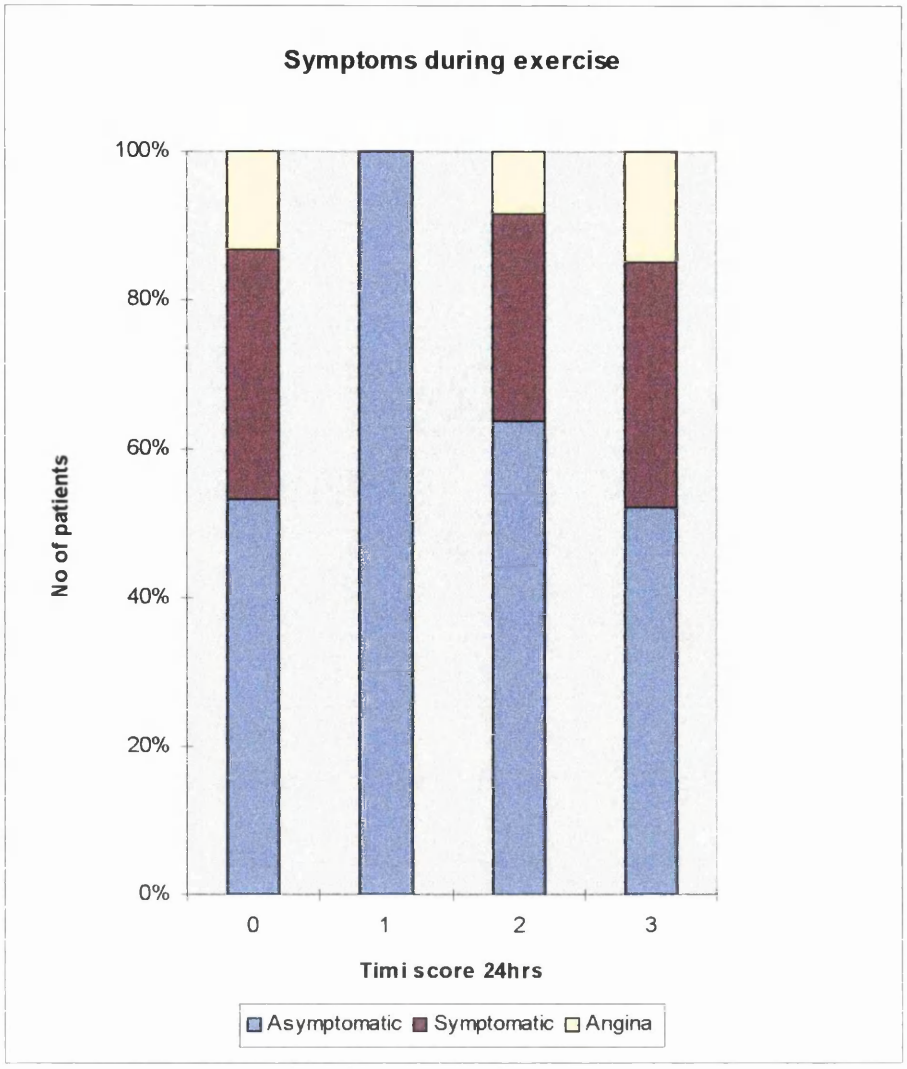

Figure 6.5 Percentage of patients with symptoms during exercise related to TIMI score at 24 hrs.

Symptoms	TIMI Score at 24hrs			
	0	1	2	3
Asymptomatic	8	6	23	46
Symptomatic	7	0	13	42
(X^2 = 6.110, NS)				
No Angina	13	6	33	75
Angina	2	0	3	13
(X^2 = 1.864, NS)				

Table 6.5 Symptoms reported during exercise related to TIMI score at 24 hrs

6.2.2 ST-T Changes during Exercise Testing

As shown in table 6.6 patients with TIMI score of 0 had a greater incidence of ST segment depression during the exercise test, with 60% of patients showing evidence of reversible ischemia, $p < 0.05$. This is illustrated in and fig 6.6. There was no relationship between the occurrence of ST elevation and T wave normalisation and the TIMI score at 24 hrs

Symptoms	TIMI SCORE AT 24 HRS			
	0	1	2	3
ST Depression				
No ST ↓	6	6	25	52
ST ↓	9	0	11	36
(X^2 = 7.800, p<0.05)				
ST Elevation				
No ST↑	13	5	25	65
ST ↑	2	1	11	22
(X^2 = 1.908, NS)				
T Wave Normalisation				
No T↑	12	2	18	51
T ↑	3	4	18	37
(X^2 = 5.365, NS)				

Table 6.6 ST-T changes during exercise and TIMI score at 24 hrs

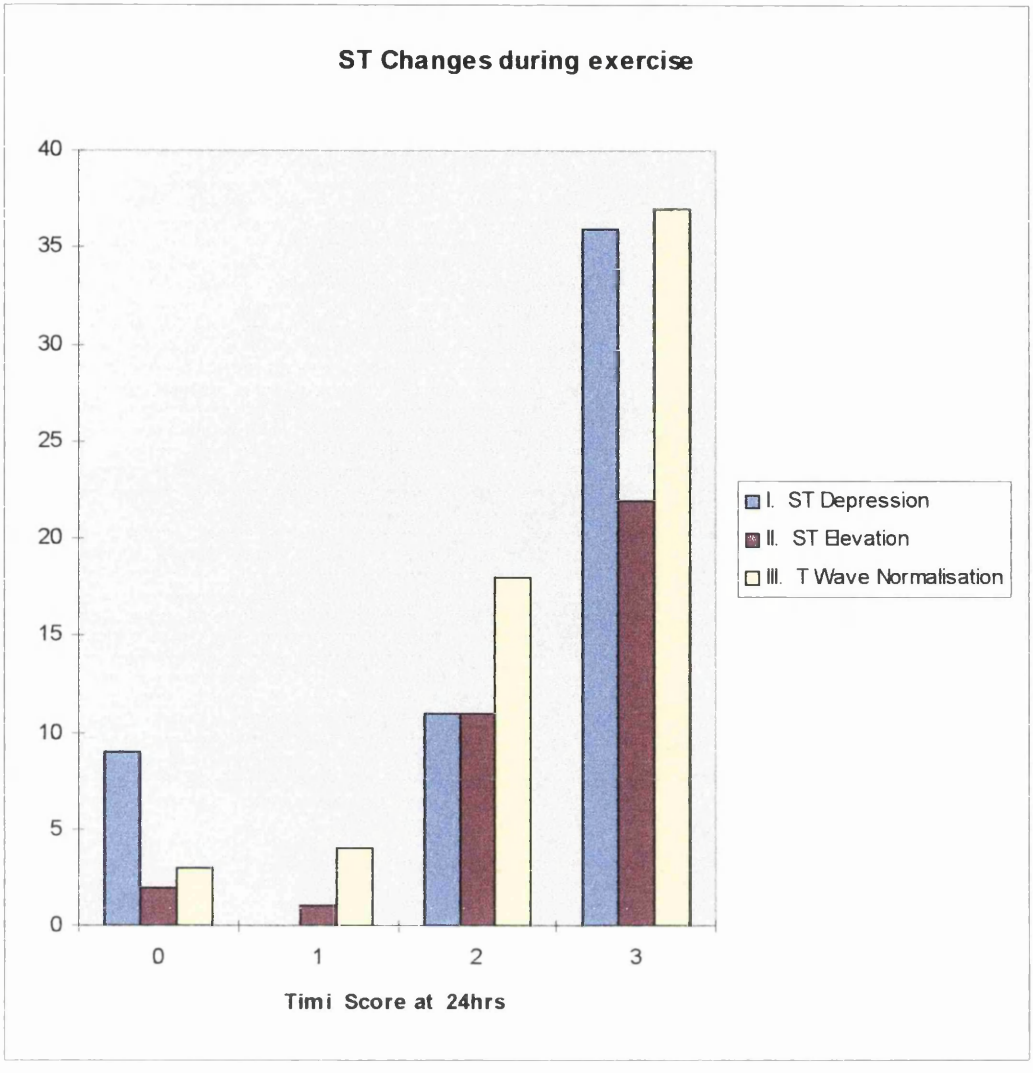

Figure 6.6 No of patients with ST changes during exercise testing related to TIMI score at 24hrs

6.2.3 Functional Capacity

Analysis of variance failed to show any relationship between TIMI score at 24 hrs and

1. Total exercise time
2. Metabolic equivalents achieved during exercise
3. Failure to achieve median exercise capacity
4. Failure of Systolic blood pressure to increase by ≥ 30mmhg
5. Failure of rate pressure product to increase by ≥ 8500

6.3 Coronary Patency

TIMI scores 0 and 1 were combined to define those vessels which were non patent, and similarly TIMI scores 2 and 3 were combined to define patent arteries at 90 mins and 24 hrs. Table 6.7 and table 6.8 show the distribution of coronary patency within these groups respectively. 62% patients and 83% patients had patent arteries at 90 mins and 24 hrs respectively. This is illustrated in fig 6.7.

Patency Group at 90 Mins	No.of Patients	%
Non-Patent (0,1)	74	38
Patent (2,3)	120	120
Total No. of patients	194	

Table 6.7 The distribution of patients within each patency group undergoing angiography at 90 mins.

Patency Group at 24 hrs	No.of Patients	%
Non-Patent (0,1)	31	17
Patent (2,3)	156	83
Total No. of patients	187	

Table 6.8 The distribution of patients within each patency group undergoing angiography at and 24 hrs.

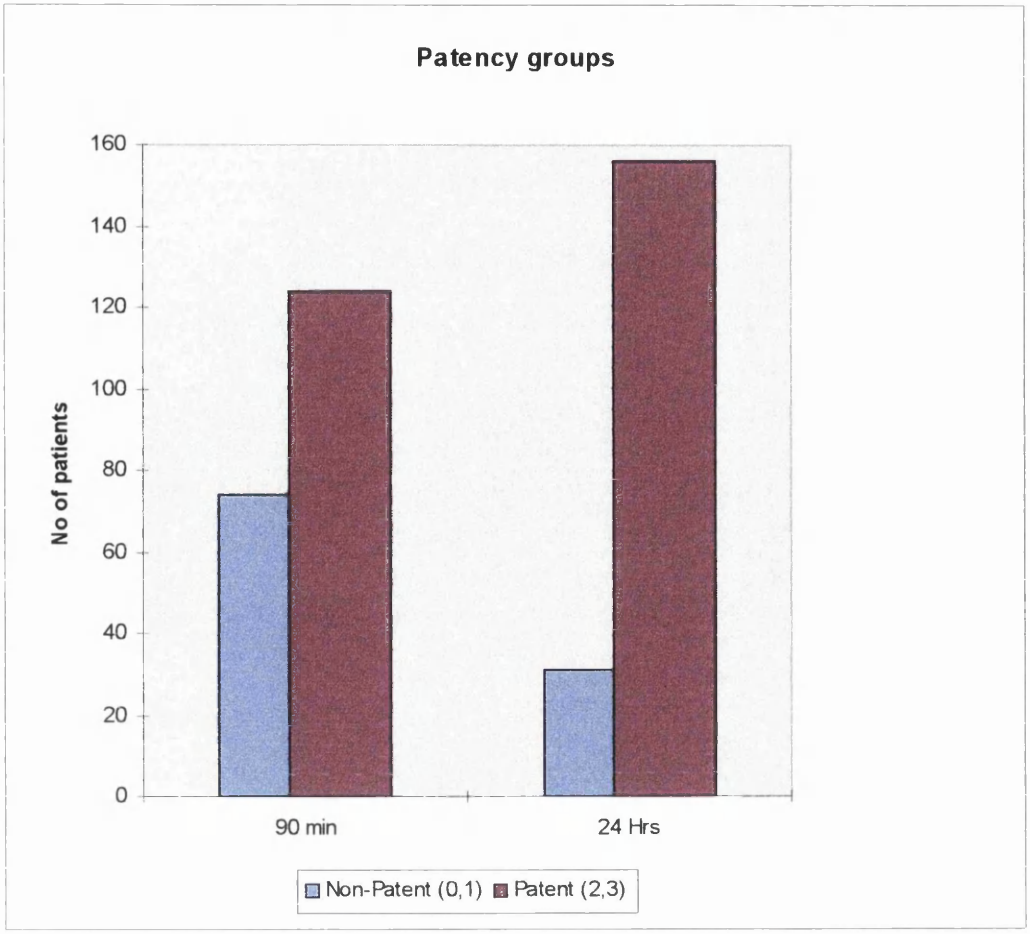

Figure 6.7 Patency Groups at 90 min and 24 hrs

6.3.1 Symptoms Reported During Exercise Testing

As shown by X^2 analysis in table 6.9 and table 6.10 patency group at 90 mins or 24 hrs did not affect the development of any symptoms, nor the development of angina during exercise teasing. This is illustrated in figs 6.8 and 6.9.

Symptoms	Patency Group (2,3) 90 mins	Patency Group (2,3) 24 hrs
Asymptomatic	54	69
Symptomatic	41	55
Total Patent	95	124
Total no of Patients	148	145
X^2	0.001	0.891
P Value	NS	NS

Table 6.9 Patency and all Symptoms Combined during Exercise

Angina	Patency Group (2,3) 90 mins	Patency Group (2,3) 24 hrs
No Angina	82	108
Angina	13	16
Total Patent	95	124
Total No. of Patients	148	145
X^2	0.170	0.189
P Value	NS	NS

Table 6.10 Patency and Angina during Exercise Testing

6.3.2 ST-T Changes During Exercise Testing

As shown in table 6.11 coronary angiography identified patency of the infarct related artery in 95 of the 148 patients at 90mins and 124 of 145 patients at 24hrs. Patency of the infarct related vessel did not affect the development of ST depression, ST elevation or T wave normalisation during exercise.

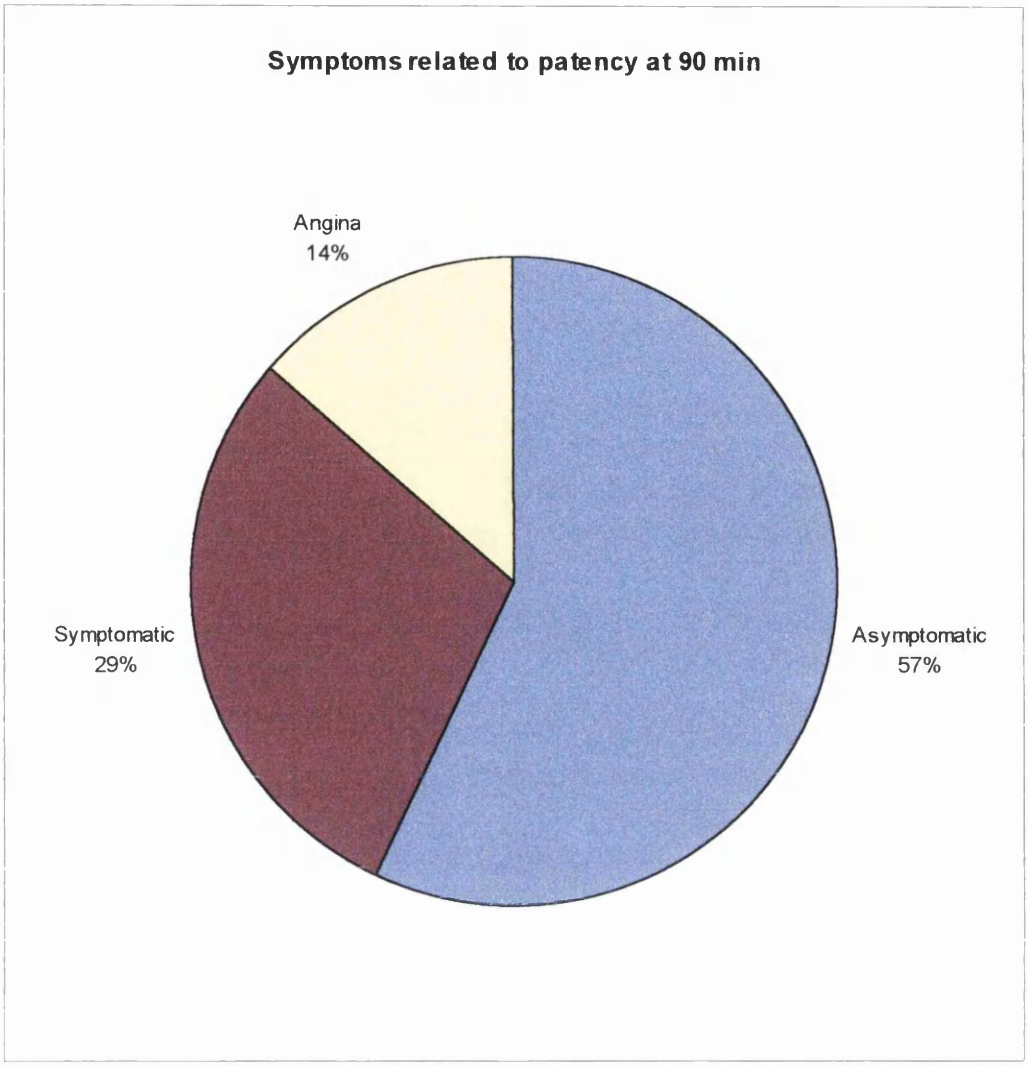

Figure 6.8 Patent infarct related artery at 90 mins and symptoms during exercise testing

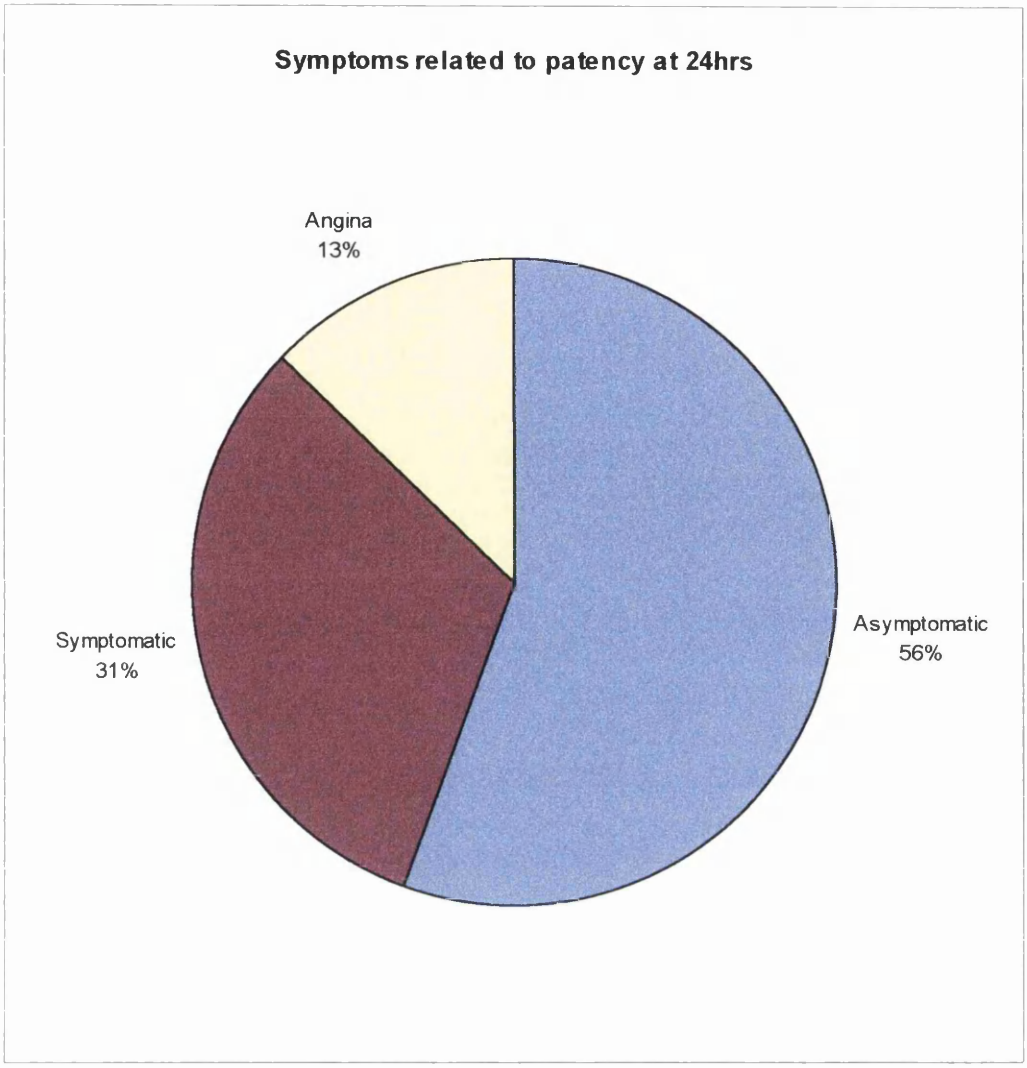

Figure 6.9 Patent infarct related artery at 24hrs and Symptoms during Exercise Testing

ST -T Changes	Patency Group (2,3) 90 mins n=95/148	Patency Group (2,3) 24 hrs n=124/145
ST Depression		
No ST↓	60	77
ST ↓	35	49
X^2	0.313, P=NS	0.816, P=NS
ST Elevation		
No ST ↑	71	90
ST ↑	23	33
X^2	0.996, P=NS	1.505, P=NS
T Wave Normalisation		
No T ↑	53	69
T ↑	42	55
X^2	0.107, P=NS	0.891, P=NS

Table 6.11 Patency and ST -T changes during Exercise Testing

6.3.3 Functional Capacity

Analysis of variance failed to show any relationship between patency at 90 mins and 24 hrs and exercise capacity, change in systolic blood pressure or rate pressure product.

6.3.4 Clinical Outcome

Patency (TIMI score 2,3) at 90 mins and 24 hrs was used to predict clinical outcome by Kaplan Meier event free survival analysis. Tables 6.12, 6.13 and 6.14 below show the event-free survival analysis for in-hospital events, outpatient events and overall events. As shown, ischemic pain post infarct was significantly more common in patients with non patent arteries at 24 hrs (13% v 7%,p=0.0124). This is illustrated in fig 6.10. There was a trend towards the development of acute left ventricular failure in the peri infarct period if the infarct related artery was non patent at 24hrs (22%v 11%,p=0.079). 30% of patients with non patent vessels at 90 mins following thrombolysis developed chronic heart failure as an outpatient post hospital discharge compared to 15% of patients with patent arteries (p=0.021).This is illustrated in fig 6.11

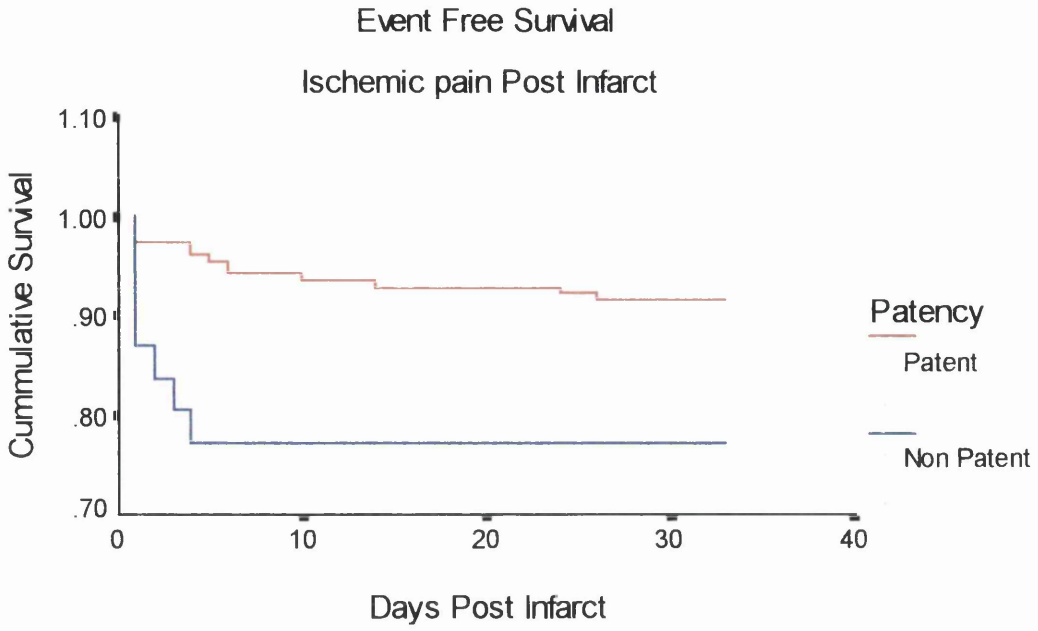

Figure 6.10 Patency at 24hrs and Ischemic pain Post Infarct

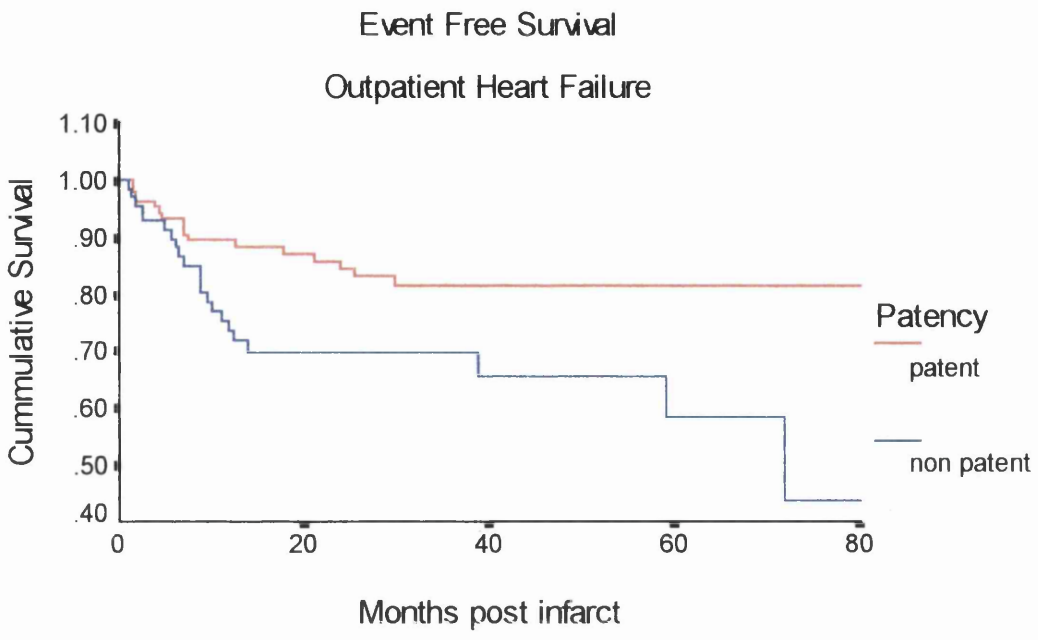

Figure 6.11 Patency at 90 min and Congestive Cardiac Failure as an Outpatient

The development of heart failure overall, either acute left ventricular failure or chronic heart failure was significantly more common in patients with non patent vessels at 90 mins (40% v 21%,P=0.028). This is illustrated in figure 6.12.

	Time	Patency (TIMI) n=	Events	%	P Value
Ischemic pain	90 mins	(0, 1) 74	10	13	
		(2, 3) 120	9	7	0.186
	24 hrs	(0, 1) 31	7	22	
		(2, 3) 156	13	8	**0.012**
Acute LVF	90 mins	(0, 1)	11	15	
		(2, 3)	14	12	0.477
	24 hrs	(0, 1)	7	22	
		(2, 3)	17	11	0.079
All Cardiac Events	90 mins	(0, 1)	16	20	
		(2, 3)	15	12	0.110
	24 hrs	(0, 1)	8	25	
		(2, 3)	22	14	0.076

Table 6.12 TIMI Scores and In Hospital Events

	Time	Patency (TIMI) n=	Events	%	P Value
Angina	90 mins	(0, 1) 72	32	42	
		(2, 3) 116	44	38	0.820
	24 hrs	(0, 1) 31	9	29	
		(2, 3) 151	60	39	0.164
All Cardiac Events	90 mins	(0, 1)	25	34	
		(2, 3)	44	38	0.456
	24 hrs	(0, 1)	10	32	
		(2, 3)	56	37	0.361
Heart failure	90 mins	(0, 1)	22	30	
		(2, 3)	17	15	**0.021**
	24 hrs	(0, 1)	6	19	
		(2, 3)	35	23	0.585

Table 6.13 TIMI Scores and Outpatient Cardiac Events

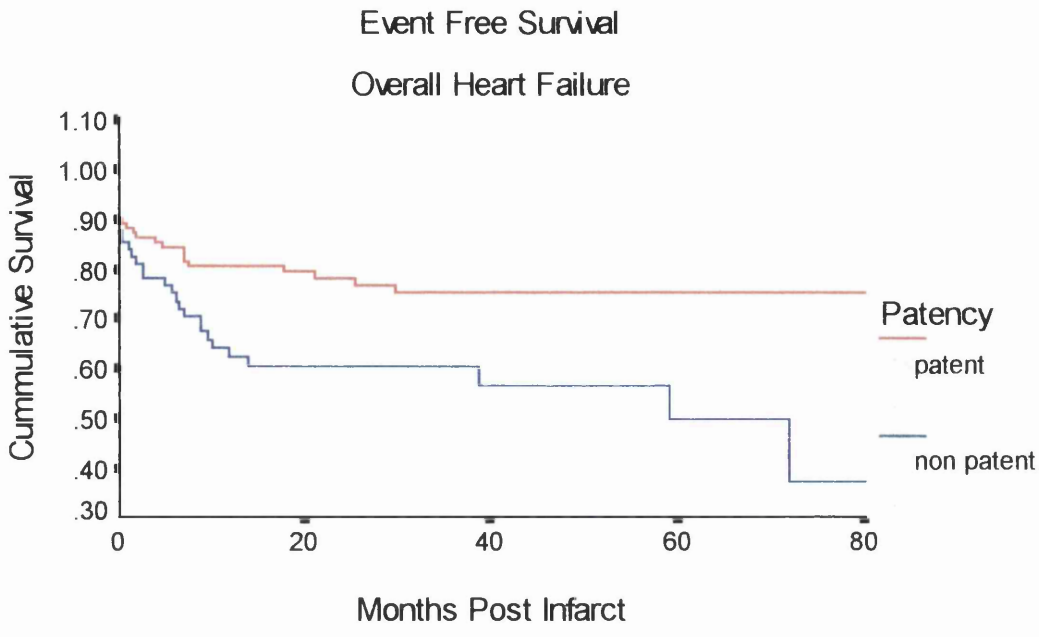

Figure 6.12 Patency at 90 min and Heart Failure Overall

	Time	Patency (TIMI) N=	Events	%	P Value
Mortality	90 mins	(0, 1) 74	9	12	
		(2, 3) 116	7	6	0.164
	24 hrs	(0, 1) 31	4	13	
		(2, 3) 152	9	6	0.241
Heart failure	90 mins	(0, 1)	30	40	
		(2, 3)	26	21	**0.028**
	24 hrs	(0, 1)	11	35	
		(2, 3)	45	29	0.211
All cardiac events	90 mins	(0, 1)	36	49	
		(2, 3)	51	44	0.422
	24 hrs	(0, 1)	15	48	
		(2, 3)	69	45	0.585

Table 6.14 TIMI Scores and Overall Cardiac Events

6.4 The Effect Of Patency On Exercise Variables TIMI Score 3 V (0, 1,2)

Following angiography at 90 mins and 24 hrs, those patients with a TIMI score of 3 were identified and compared against those with TIMI score 0,1,2 to determine the effect of full patency. Table 6.15 below shows the distribution of patients with TIMI score 3 within patients undergoing angiography at 90 mins and 24 hrs. As shown, 36% patients and 58% patients had TIMI score 3 at 90 mins and 24 hrs respectively.

TIMI Score 3 at 90 Mins	No. of Patients	%
TIMI (0,1,2)	125	64
TIMI (3)	69	36
Total	194	

Table 6.15 TIMI Score 3 at 90 min

TIMI Score 3 at 24 hrs	No. of Patients	%
TIMI (0,1,2)	78	42
TIMI 3	109	58
Total	187	

Table 6.16 TIMI Score 3 at 24hrs

6.4.1 All Symptoms Reported During Exercise Testing

148 of 194 patients and 145 of 187 patients assessed invasively for vessel patency at 90 mins and 24hrs post thrombolysis respectively underwent exercise testing. X^2 analysis was performed to determine whether there was any relationship between TIMI score 3 at 90 mins and symptoms reported during exercise. As shown in Table 6.17, TIMI 3 score at 90 mins or 24 hrs was not related to the development of any symptoms, nor the development of angina during exercise.

Symptoms	TIMI Score 3 90 mins	TIMI Score 3 24 hrs
Asymptomatic	32	46
Symptomatic	26	42
X^2	0.098,NS	2.258,NS
No Angina	49	75
Angina	9	13
X^2	0.612,NS	1.146,NS

Table 6.17 TIMI Score 3 and Symptoms Reported During Exercis

6.4.2 ST-T Changes During Exercise Testing

As shown in table 6.18, there was no relationship between TIMI score 3 at 90 mins or 24 hrs and the development of ST-T changes during exercise.

6.4.3 Functional Capacity

Analysis of variance failed to show any relationship between full patency TIMI score 3 at 90 mins and 24 hrs and exercise capacity, change in systolic blood pressure or rate pressure product.

6.4.4 Clinical Outcome

The predictive value of full patency, TIMI score 3, in clinical events was determined for in-hospital events, outpatient events and overall events. The results of Kaplan Meier event-free survival analysis are shown in tables 6.19,6.20 and 6.21. The development of peri infarct acute left ventricular failure was less common in patients with TIMI score 3 at 24 hrs compared to patients with TIMI score 0,1,2 (9 % v 28%) although this did not

reach statistical significance , p=0.072. This is illustrated in fig 6.13. The development of chronic heart failure in 5 years of follow up was significantly less common in patients with TIMI score 3 at 90 mins (13% v 24%.p=0.019) and 24 hrs (18% v 30%,p=0.054). This is illustrated in fig 6.14 and 6.15 respectively. Cardiac death was also reduced in those patients with TIMI score 3 at 90 mins compared to TIMI score 0,1,2 combined (4% v 10%,p=0.0694). This is illustrated in figure 6.16. Overall heart failure was significantly less common in patients with TIMI score 3 at 24 hrs compared to TIMI score 0,1,2 (p=0.007). This is illustrated in fig 6.17.

ST - T Changes	TIMI Score 3 90 mins	TIMI Score 3 24 hrs
ST Depression		
No ST ↓	35	52
ST ↓	23	36
X^2	0.052,NS	0.495,NS
ST Elevation		
No ST ↓	44	65
ST ↓	14	22
X^2	0.457,NS	0.010,NS
T Wave Normalisation		
No T ↑	34	51
T ↑	24	37
X^2	0.135,NS	0.047,NS

Table 6.18 TIMI score 3 at 90 min and 24 hrs and ST-T changes during exercise

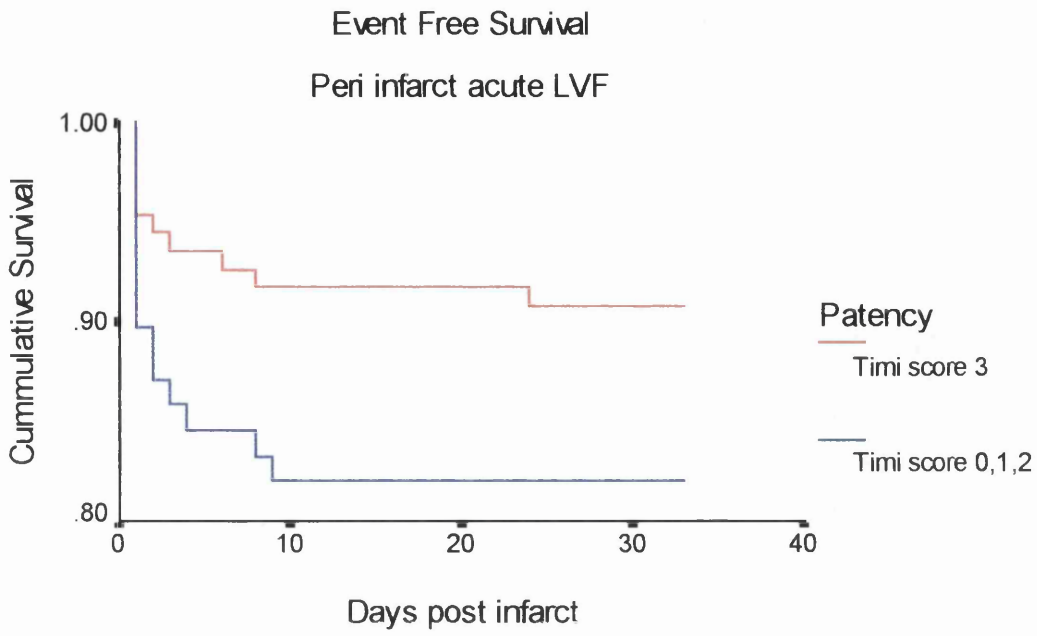

Figure 6.13 TIMI Score 3 and Peri Infarct Acute Left Ventricular Failure

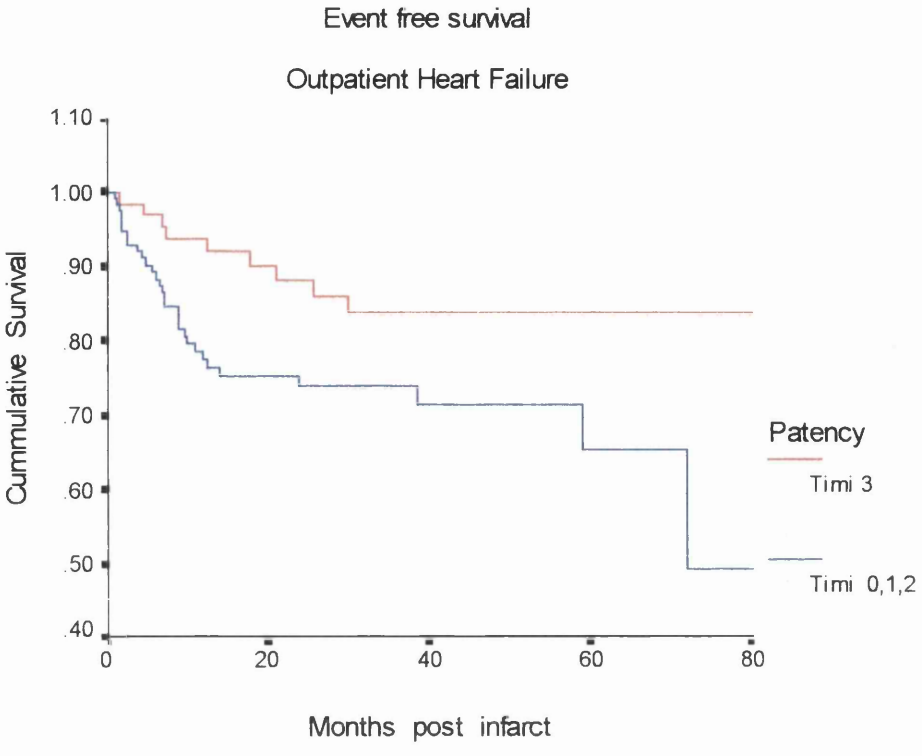

Figure 6.14 TIMI Score 3 at 90 min and Outpatient heart failure

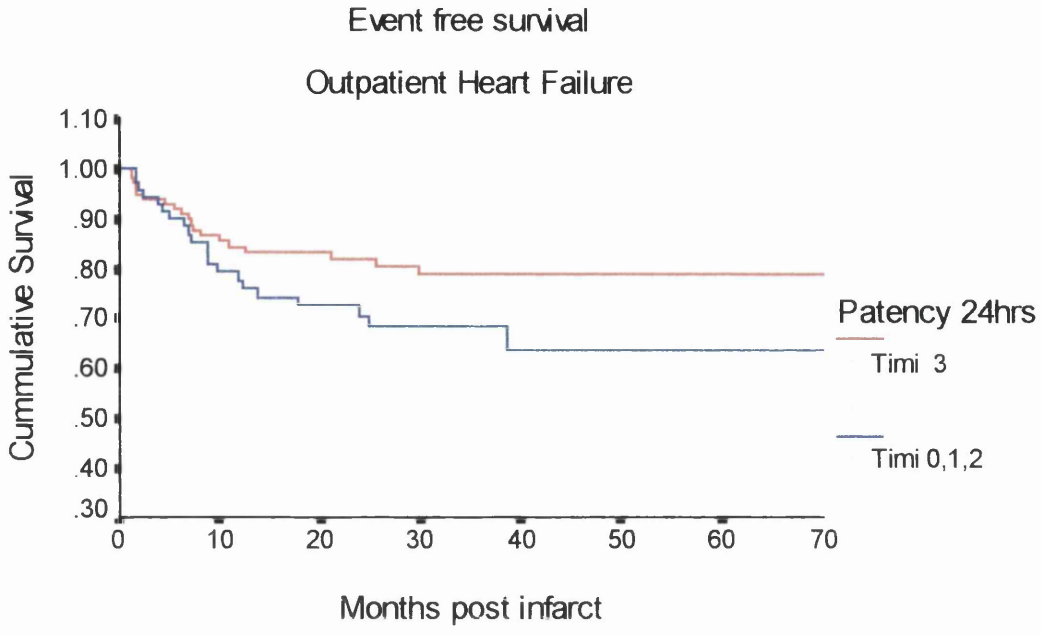

Figure 6.15 TIMI Score 3 at 24 hrs and Congestive Cardiac Failure as an Outpatient

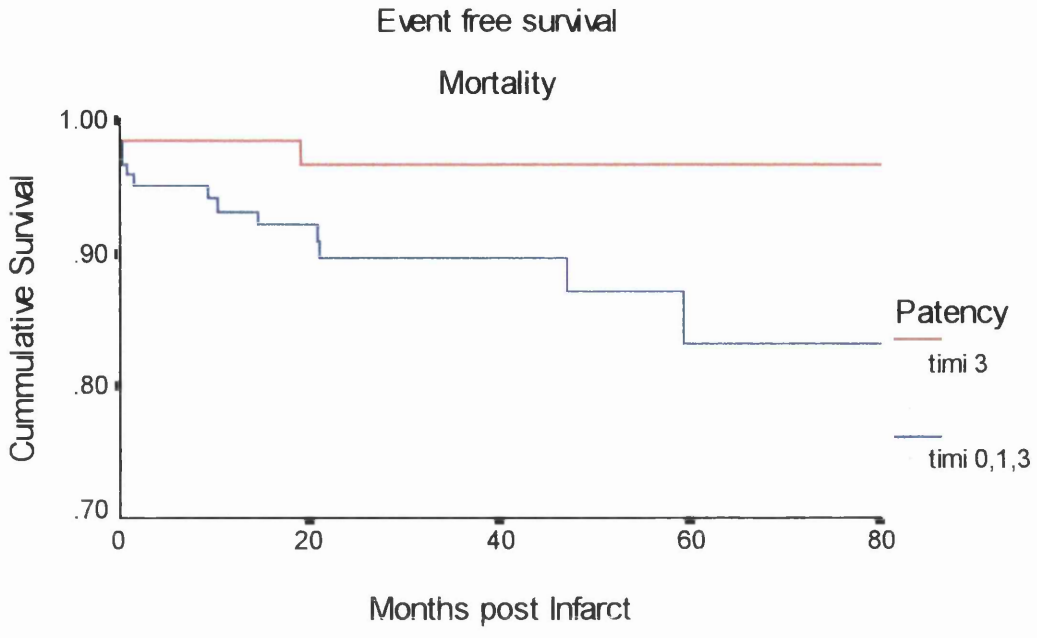

Figure 6.16 Patency Groups and Mortality

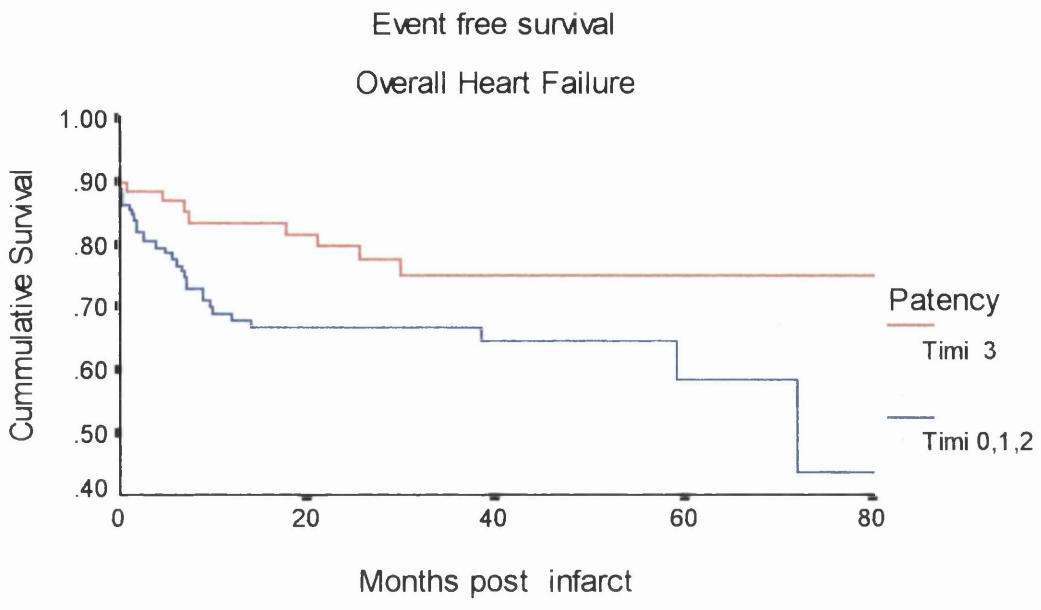

Figure 6.17 TIMI Score 3 and overall Heart failure

	Time	Patency (TIMI) N=	Events	%	P Value
Ischemic pain	90 min	(0,1,2) 125	12	9	
		(3) 69	7	10	0.687
	24 hrs	(0,1,2) 78	7	22	
		(3) 109	13	8	0.206
Acute LVF	90 min	(0,1,2)	17	14	
		(3)	8	11	0.689
	24 hrs	(0,1,2)	14	28	
		(3)	10	9	0.072
All Cardiac Events	90 min	(0, 1)	21	17	
		(2, 3)	10	14	0.762
	24 hrs	(0, 1)	14	18	
		(2, 3)	16	15	0.568

Table 6.19 TIMI Score 3 and In Hospital Cardiac Events

	Time	Patency (TIMI)	Events	%	P Value
Angina	90 min	0,1,2 n=120	44	37	
		3 n= 68	30	44	0.820
	24 hrs	0,1,2 n= 75	28	37	
		3 n=107	41	38	0.953
All cardiac events	90 min	0,1,2	36	30	
		3	33	48	0.183
	24 hrs	0,1,2	26	34	
		3	40	37	0.775
Heart failure	90 min	0,1,2	30	24	
		3	9	13	0.019
	24 hrs	0,1,2	22	30	
		3	19	18	0.054

Table 6.20 TIMI score 3 and Out-Patient Cardiac Events

	Time	Patency (TIMI)	Events	%	P Value
Mortality	90 min	0,1,2 n=122	13	10	
		3 n=68	3	4	0.056
	24 hrs	0,1,2 n=76	7	9	
		3 n=107	6	6	0.288
Heart failure	90 min	0,1,2	41	33	
		3	15	22	0.055
	24 hrs	0,1,2	31	40	
		3	25	23	**0.007**
All cardiac events	90 min	0,1,2	50	41	
		3	37	54	0.358
	24 hrs	0,1,2	37	30	
		3	47	44	0.351

Table 6.21 TIMI score 3 and Overall Cardiac Events

6.5 Time to Patency

Coronary artery patency of the infarct-related vessel was further assessed by combining the TIMI scores from both angiographic assessments, defining time to patency as outlined below in table 6.22. The distribution of patients within each patency group is shown in table 6.23.

TIMI Score 90 MINS	TIMI Score 24 HRS	Group
(2,3)	(2,3)	Early Patency EP)
(0,1)	(2,3)	Late Patency (LP)
(0,1)	(0,1)	Non Patent (NP)
(2,3)	(0,1)	Reocclusion (R)

Table 6.22 Time to Patency Groups

Patency Group	No. of Patients	%
Early Patency	108	60
Late Patency	44	24
Non Patent	23	13
Reocclusion	6	3
Total	181	

Table 6.23 Distribution of Patients within Patency Groups

Only 6 patients were defined as reocclusions: patency at 90 min becoming non patent at 24hrs. X^2 analysis is invalidated with such small numbers, and therefore this subgroup was not analysed separately. However, given that the exercise test occurred after angiography, it is reasonable to include those patients who reoccluded in the non patent group.

6.5.1 All Symptoms Reported During Testing

X^2 analysis was used to determine whether there was any relationship in time to patency and symptoms reported during exercise. As shown, patency group did not affect the development of any symptoms, nor the development of angina during exercise testing.

Symptoms	EP	LP	NP
Asymptomatic	51	18	14
Symptomatic	37	16	5
(X^2 = 2.246, NS)			
No Angina	77	29	17
Angina	1	5	2
(X^2 = 0.206, NS)			

Table 6.24 Patency Groups and Symptoms during Exercise Testing

6.5.2 ST-T Changes During Exercise Testing

X^2 analysis showed no relationship between ST-T changes during exercise testing and time to patency groupings, as shown in Table 6.25.

6.5.3 Functional Capacity

Analysis of variance show any relationship between (1) total time of exercise test (2) metabolic equivalents achieved during exercise (3) heart rate pre exercise (4) heart rate post exercise (5) systolic blood pressure pre exercise (6) systolic blood pressure post exercise and patency groups.

ST - T Changes	EP	LP	NP
ST Depression			
No ST ↓	56	20	12
ST ↓	32	14	7
(X^2= 0.247, NS)			
ST Elevation			
No ST ↑	66	22	16
ST ↑	21	12	3
(X^2 = 2.726, NS)			
T Wave Normalisation			
No T ↑	48	20	12
T ↑	40	12	7
(X^2 = 0.552, NS)			

Table 6.25 Patency Groups and ST-T Changes During Exercise

6.5.4 Clinical Outcome

Kaplan Meier event-free survival analysis was performed to determine whether there was any relationship between time to patency and in-hospital events, outpatient events and overall clinical events. The results are shown below in table 6.26, 6.27 and 6.28. These tables contain the multiple comparisons of the patency groups; p values are shown. Post infarct ischemic pain was more common in patients with non patent vessels compared to those with early patency and late patency (22% v 9% v 7%). This is illustrated in fig 6.18. There was a trend towards a greater incidence of acute left ventricular failure in the peri infarct period with non patency compared to early and late patency (26% v 11% v 9%). This is illustrated in fig 6.19. The development of chronic heart failure was more common in patients with late patency compared to those with early patency (36% v 15%,p=0.073). This is illustrated in fig 6.20. The development of heart failure overall (acute left ventricular failure plus chronic heart failure) was again

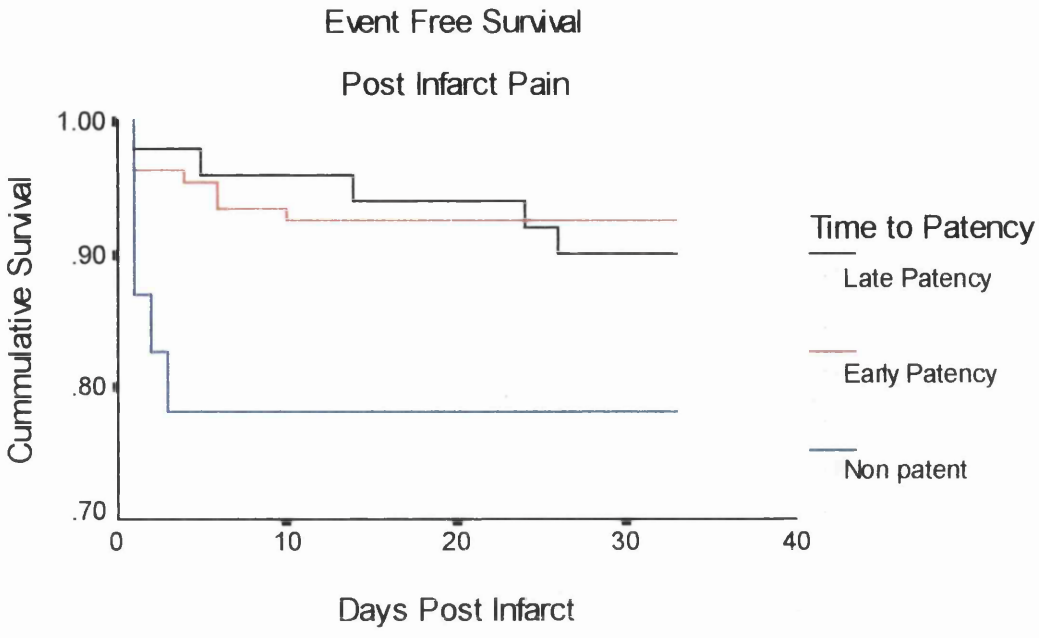

Figure 6.18 Patency Groups and Post Infarct Ischemic Pain

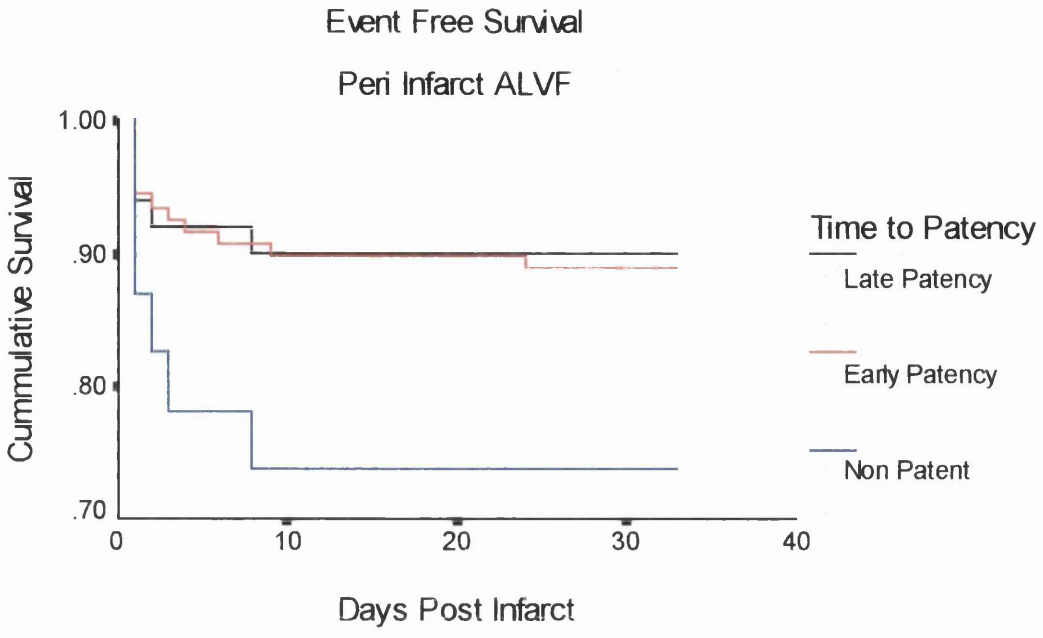

Figure 6.19 Patency Groups and Peri Infarct Acute Left Ventricular Failure

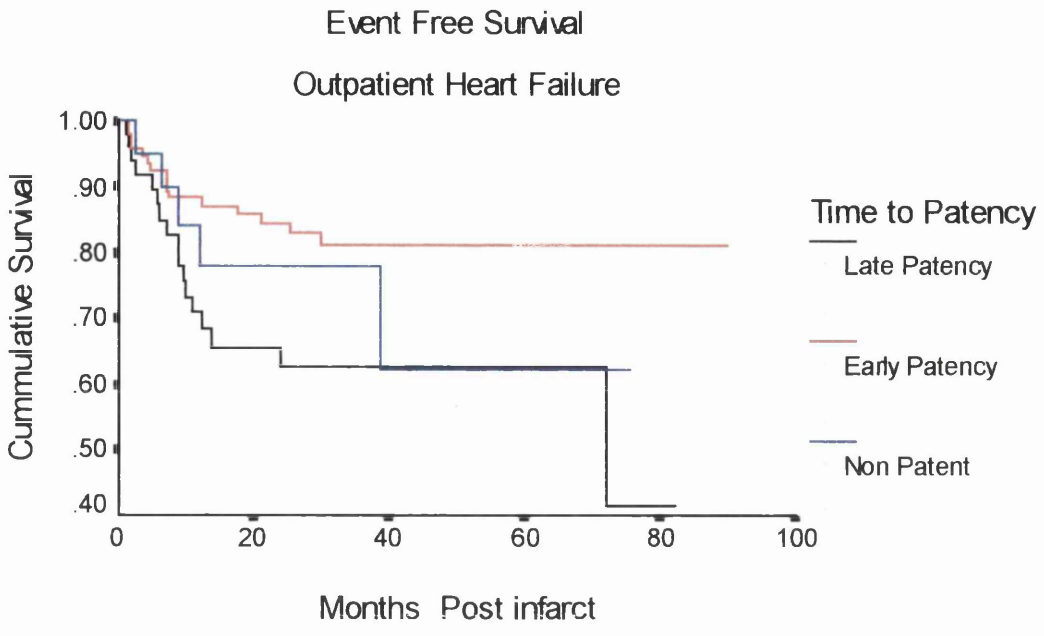

Figure 6.20 Patency Groups and Outpatient Congestive Cardiac Failure

more common in patients with late patency versus early patency but not statistically significant p=0.075.It was significantly more common in patients with non patency versus early patency (43% v 22%,p=0.027). This is illustrated in fig. 6.21.

		Patency	Events	%
Ischemic pain		**EP** n=108	8	7
		LP n=44	4	9
		NP n=23	5	22
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.814	**0.032**
	LP			0.099
Acute LVF		**EP**	12	11
		LP	4	9
		NP	6	26
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.742	0.070
	LP			0.073
All Cardiac Events		**EP**	14	11
		LP	7	9
		NP	6	26
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.583	0.210
	LP			0.831

Table 6.26 Patency Groups and In Hospital Cardiac Events

		Patency	Events	%
Angina		EP,n=104	38	36
		LP,n=43	21	48
		NP,n=29	29	6
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.308	0.379
	LP			0.104
Heart failure		EP	16	15
		LP	16	36
		NP	6	20
		EP	**LP**	**NP**
P values	**EP**		**0.007**	0.611
Multiple comparisons	**LP**			0.155
.All Cardiac Events		EP	43	41
		LP	12	27
		NP	9	31
		EP	**LP**	**NP**
P values	**EP**		0.520	0.504
Multiple comparisons	**LP**			0.253

Table 6.27 Patency Groups and Outpatient Cardiac Events

		Patency	Events	%
Mortality		EP n=104	5	5
		LP n=44	3	7
		NP n=23	3	13
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.767	0.298
	LP			0.428
Heart failure		EP	24	22
		LP	18	40
		NP	10	43
P values		**EP**	**LP**	**NP**
Multiple comparisons	EP		0.075	**0.027**
	LP			0.413
All Cardiac		EP	49	47
Ischemic Events		LP	18	23
		NP	12	52
P values		**EP**	**LP**	**NP**
Multiple comparisons	**EP**		0.964	0.471
	LP			0.409

Table 6.28 Patency Groups and Overall Cardiac Events

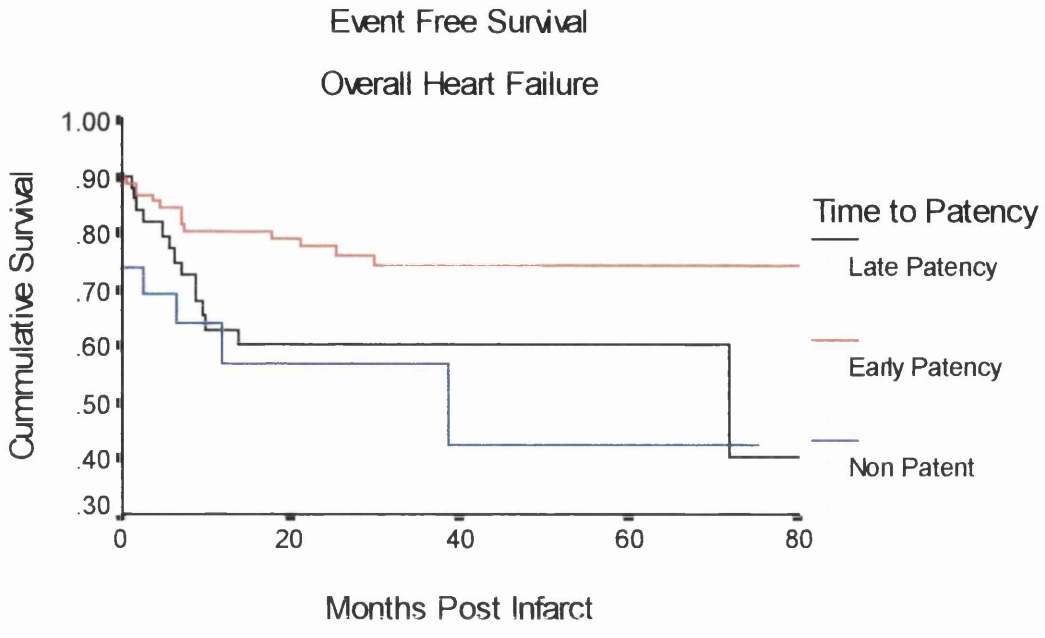

Figure 6.21 Patency Groups and Overall Heart Failure

7. PRE-DISCHARGE EXERCISE TESTING IN THE PREDICTION OF RESIDUAL STENOSIS IN THE INFARCT-RELATED ARTERY AND ADDITIONAL VESSEL DISEASE

Following thrombolysis angiography was carried out at 90 mins by the Judkins technique. On the basis of the electrical changes on the ECG on admission to Coronary Care, the presumed infarct-related artery was visualised first by standard radiographic views to define patency which was quantified by the TIMI scoring system (appendix IV). The non-infarct related artery was then visualised to define additional vessel disease. A significant stenosis was defined as stenosis ≥ 50%. The arterial sheath was left in situ and a further angiogram was performed at 24 hrs to define:

1. Patency of the infarct-related vessel by TIMI scoring
2. Any significant residual stenosis of the infarct-related vessel (≥ 50%) by TIMI scoring
3. Reocclusion of the infarct-related vessel

The effects of a significant residual stenosis of the infarct-related artery regardless of additional vessel disease, was related to the results of pre-discharge exercise testing and used to predict clinical outcome. Patients with only the infarct-related artery affected and no additional vessel disease were considered as having single vessel disease. However these patients were further divided into 3 groups outlined below and related to the results of predischarge exercise testing. Residual stenosis was similarly used to predict future cardiac events.

1. Significant residual stenosis ≥ 50%
2. No significant residual stenosis
3. Total Occlusion of the infarct related vessel

7.1 Residual Stenosis in the Infarct-Related Artery ± Additional Vessel Disease

Table 7.1 shows the number of patients with a significant residual stenosis, no significant residual stenosis and occlusion of the infarct-related artery with or without additional vessel disease following angiography at 24 hrs. As shown 72% of patients had a significant residual stenosis of the infarct-related artery at 24 hrs following thrombolysis. Only 13% of patients had persistent coronary occlusion at angiography at 24 hrs post thrombolysis. This is illustrated in and fig 7.1.

Stenosis of Infarct-Related Artery	No. of Patients	%
No stenosis	28	15
Stenosis ≥ 50%	134	72
Occluded Vessels	24	13
Total	186	

Table 7.1 Infarct vessel status following 24 hr angiogram

7.1.1 Symptoms during exercise Testing

147 of the 186 patients who had infarct vessel status determined by angiography at 24 hrs post thrombolysis were exercised prior to discharge. As shown by X^2 analysis in table 7.2 there was no relationship between residual stenosis and the development of symptoms during exercise testing. This is illustrated in Fig 7.2.

Symptoms	No Stenosis	Stenosis	Occlusion
Asymptomatic	15	59	10
Symptomatic	11	46	6
($X^2 = 0.230$, NS)			
No angina	23	92	14
angina	3	13	2
($X^2 = 0.015$,NS)			

Table 7.2 Symptoms during exercise testing related to the presence of a stenosis in the infarct related artery

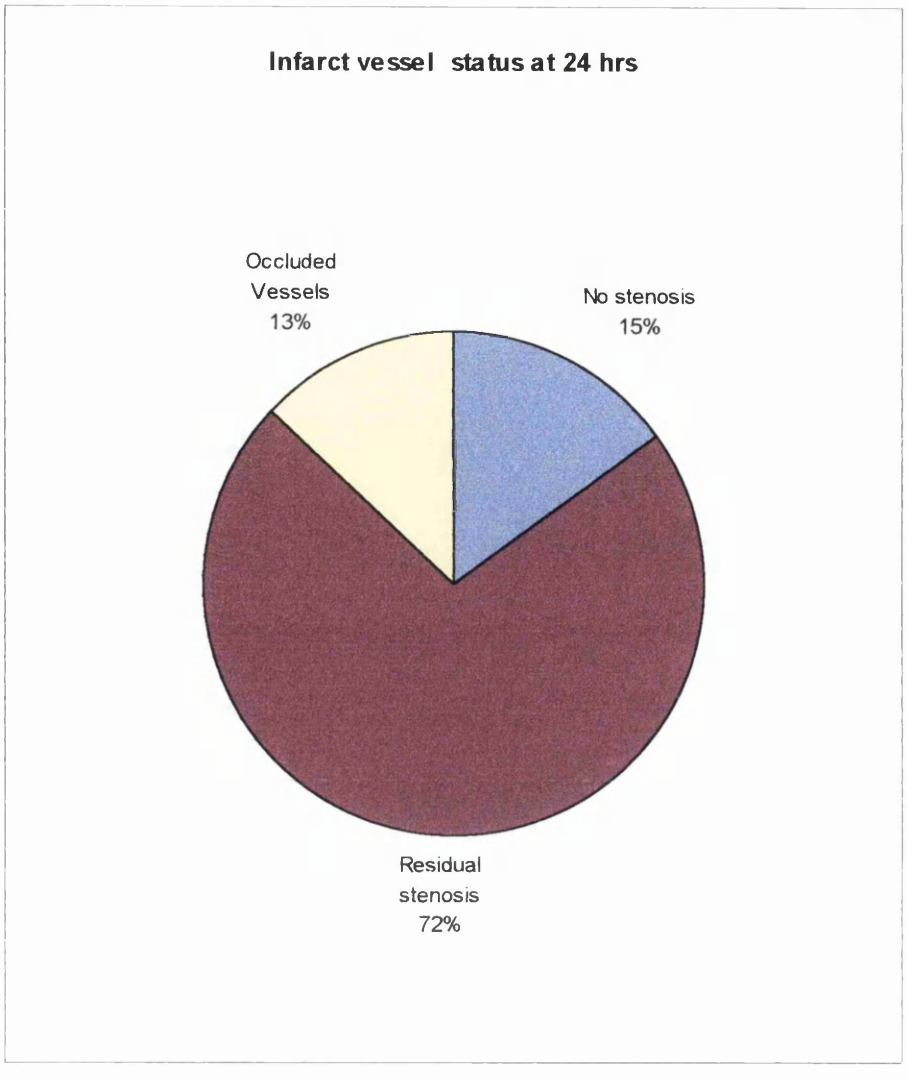

Figure 7-1 Percentage of patients with residual stenosis of infarct related vesselregardless of additional vessel disease

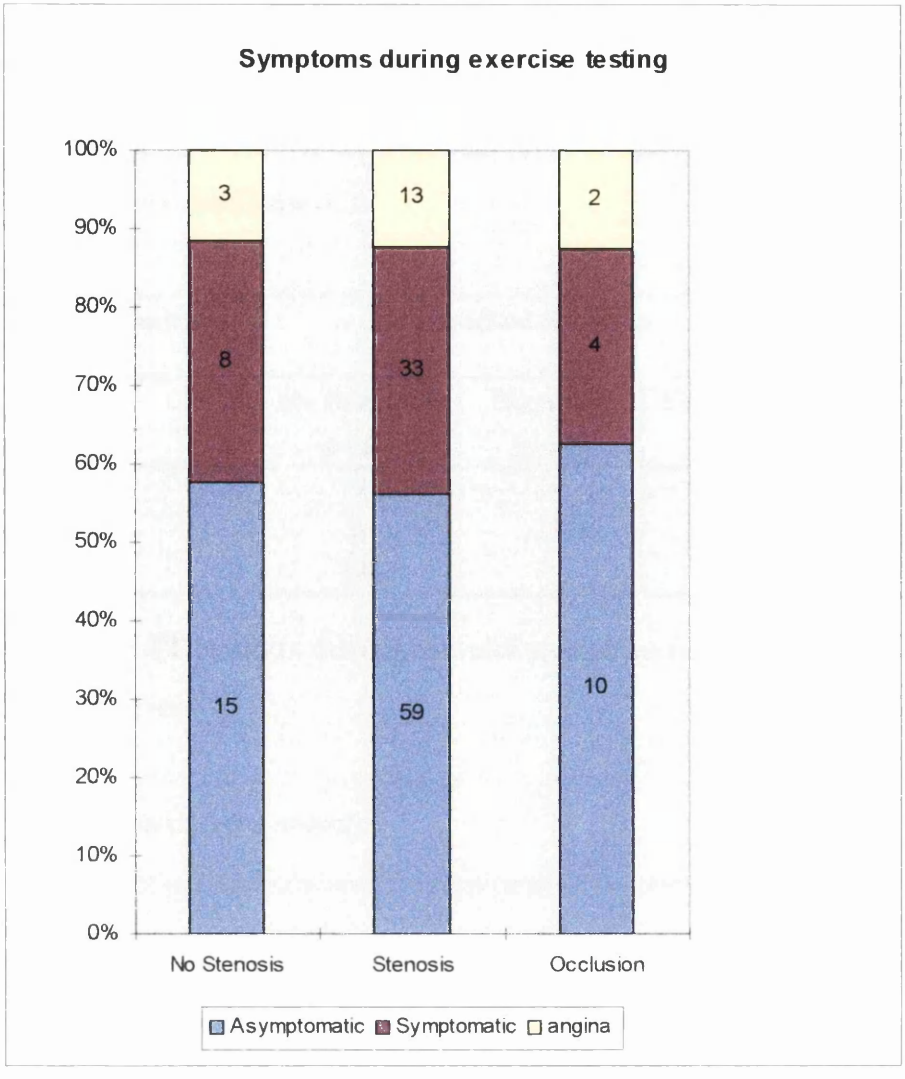

Figure 7-2 Residual Stenosis regardless of additional vessel disease and all Symptoms during Exercise Testing

7.1.2 ST-T Changes During Exercise

As shown in table 7.3 a significant residual stenosis or a completely occluded infarct-related did not affect the development of ST-T changes during exercise. This is illustrated in and figure 7.3.

.

ST-T Changes	Residual Stenosis				
	No Stenosis n=26	Stenosis n=105	Occlusion n=16	χ^2	P Value
ST↓	9	39	9	2.365	NS
ST↑	6	29	3	0.744	NS
T ↑	14	45	4	3.365	NS

Table 7.3 ST changes during exercise related to residual stenosis of the infarct related artery.

7.1.3 Functional Capacity

Analysis of variance showed no significant relationship between residual stenosis of the infarct-related artery and other exercise variables: total exercise time, metabolic equivalents ,systolic blood pressure response or rate pressure product.

7.1.4 Clinical Outcome

Residual stenosis of infarct related artery regardless of additional vessel disease, was used to predict clinical outcome by Kaplan Meier event-free survival analysis of in hospital, outpatient and overall cardiac events shown in table 7.4, 7.5, and 7.6.

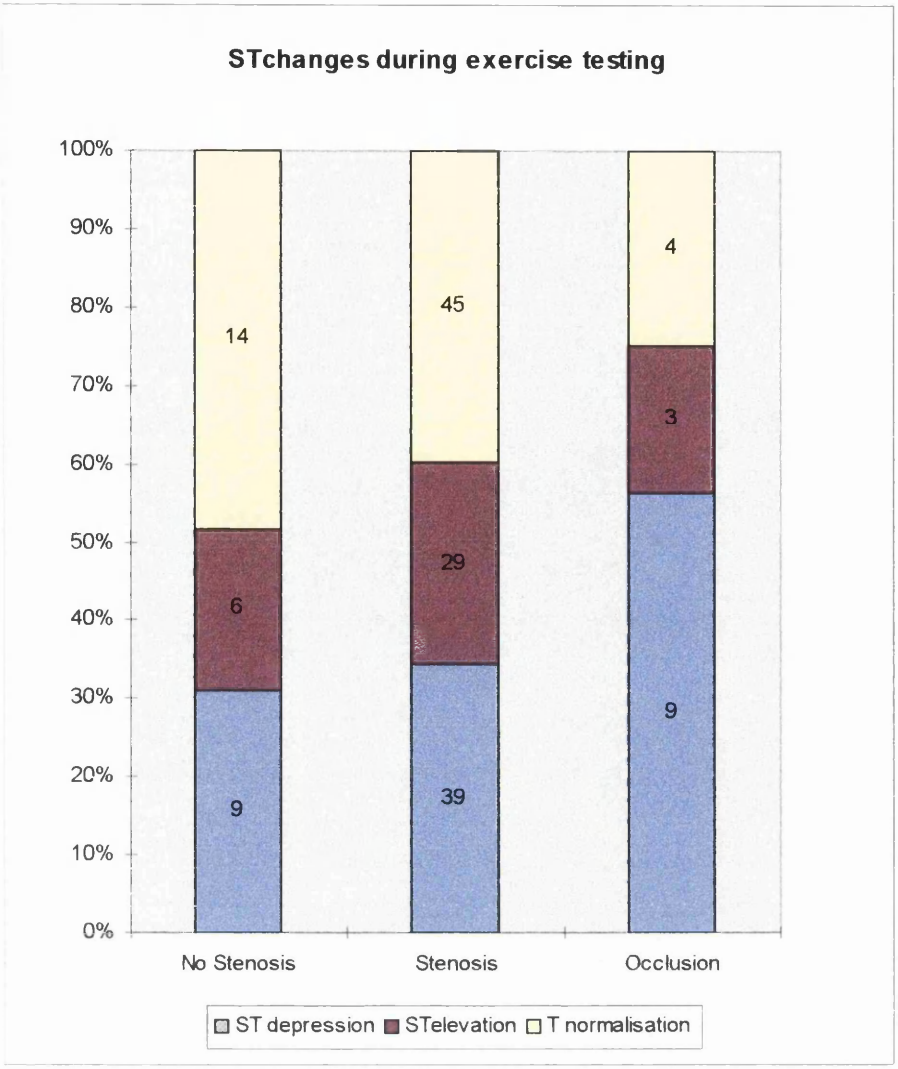

Figure 7-3 The percentage of patients with stensois,no stenosis or occlusion of the infarct related artery with ST changes during exercise.

	Residual Stenosis	Total No. Patients	Total No. Events	%
Ischemic Pain	No Stenosis	28	0	0
	Stenosis	134	15	11
	Occlusion	24	5	20
P Values		No Stenosis	Stenosis	
	Stenosis	0.064		
	Occlusion	**0.012**	0.1491	
	Overall	**0.043**		
Left Ventricular Failure	No Stenosis	28	3	11
	Stenosis	134	14	10
	Occlusion	24	6	25
P Values		No Stenosis	Stenosis	
	Stenosis	0.993		
	Occlusion	0.159	0.0423	
	Occlusion	0.115		
All Cardiac Events	No Stenosis	28	1	4
	Stenosis	134	23	17
	Occlusion	24	6	25
P Values		No Stenosis	Stenosis	
	Stenosis	0.065		
	Occlusion	0.022	0.2980	
	Overall	0.080		

Table 7.4 Residual stenosis in the prediction of in hospital events.

	Residual Stenosis	Total No. of Patients	Total No. of Events	%
Angina	No Stenosis	28	13	48
	Stenosis	134	50	38
	Occlusion	24	6	17
P Values		No Stenosis	Stenosis	
	Stenosis	0.841		
	Occlusion	0.211	0.196	
	Overall	0.405		
Heart Failure	No Stenosis	28	5	18
	Stenosis	134	29	22
	Occlusion	24	5	20
P Values		No Stenosis	Stenosis	
	Stenosis	0.720		
	Occlusion	0.962	0.683	
	Overall	0.881		
All Cardiac Events	No Stenosis	28	9	33
	Stenosis	134	48	36
	Occlusion	24	9	37
P Values		No Stenosis	Stenosis	
	Stenosis	0.5269		
	Occlusion	0.8765	0.364	
	Overall	0.5914		

Table 7.5 Residual stenosis in the prediction of outpatient cardiac events.

	Residual Stenosis	Total No. of Patients	Total No. of Events	%
Mortality	No Stenosis	28	0	0
	Stenosis	134	10	8
	Occlusion	24	3	12
P Values		No Stenosis	Stenosis	
	Stenosis	0.1577		
	Occlusion	0.0671	0.540	
	Overall	0.2568		
Heart Failure	No Stenosis	28	6	21
	Stenosis	134	38	28
	Occlusion	24	10	42
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.6561		
	Occlusion	0.1311	0.081	
	Overall	0.1739		
All Cardiac Events	No Stenosis	28	10	33
	Stenosis	134	62	36
	Occlusion	24	12	37
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.102		
	Occlusion	0.178	0.8429	
	Overall	0.245		

Table 7.6 Residual Stenosis and Overall Cardiac Events

Ischemic pain post-infarct was more common in patients with occluded infarct-related arteries at 24 hrs compared to arteries with no significant stenosis (20% v 0%,p=0.012). This is illustrated in fig 7.4. Similarly, the development of peri-infarct acute left ventricular failure was more common in patients with occluded arteries compared to those patients who had a residual stenosis post-infarct (25% v 10%,p=0.0423). This is illustrated in fig 7.5. The development of in hospital cardiac events (between day 1 and hospital discharge) was less common in patients with no residual stenosis in the infarct-related artery when compared to patients with a stenosis or an occluded vessel (4% v 17% v 25%). This is illustrated in figure 7.6. As shown the degree of residual stenosis in the infarct-related artery ± additional vessel disease did not affect out-patient events : post-infarct angina, all cardiac events or heart failure. In addition, it did not affect overall mortality from sudden cardiac death, heart failure or overall cardiac events.

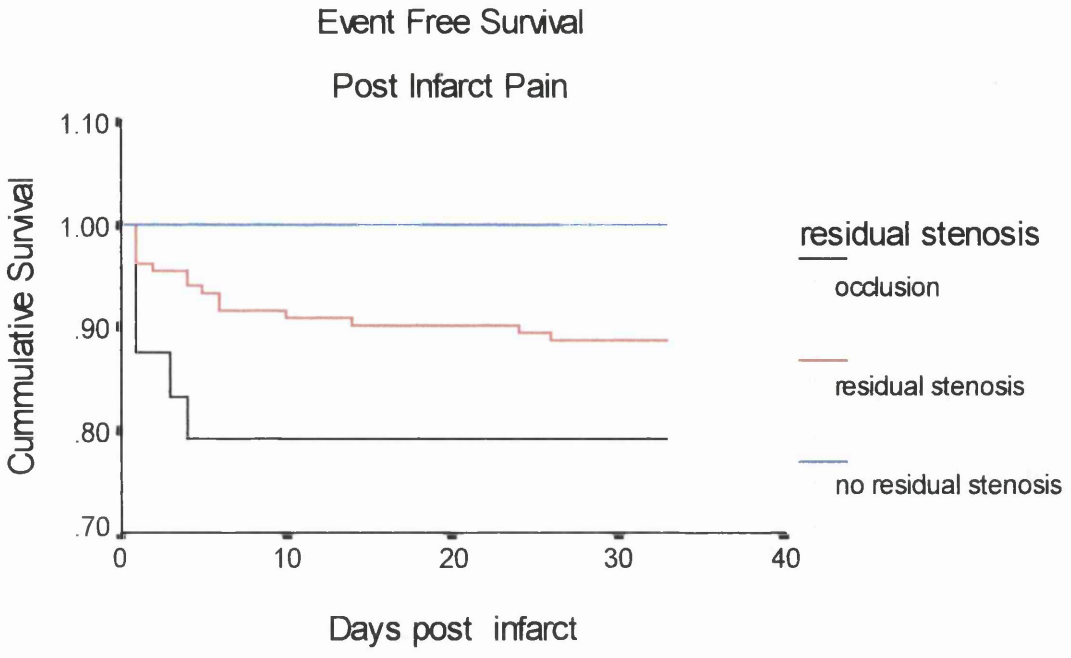

Figure 7-4 Event free survival for ischemic pain post infarct in relation to residual stenosis.

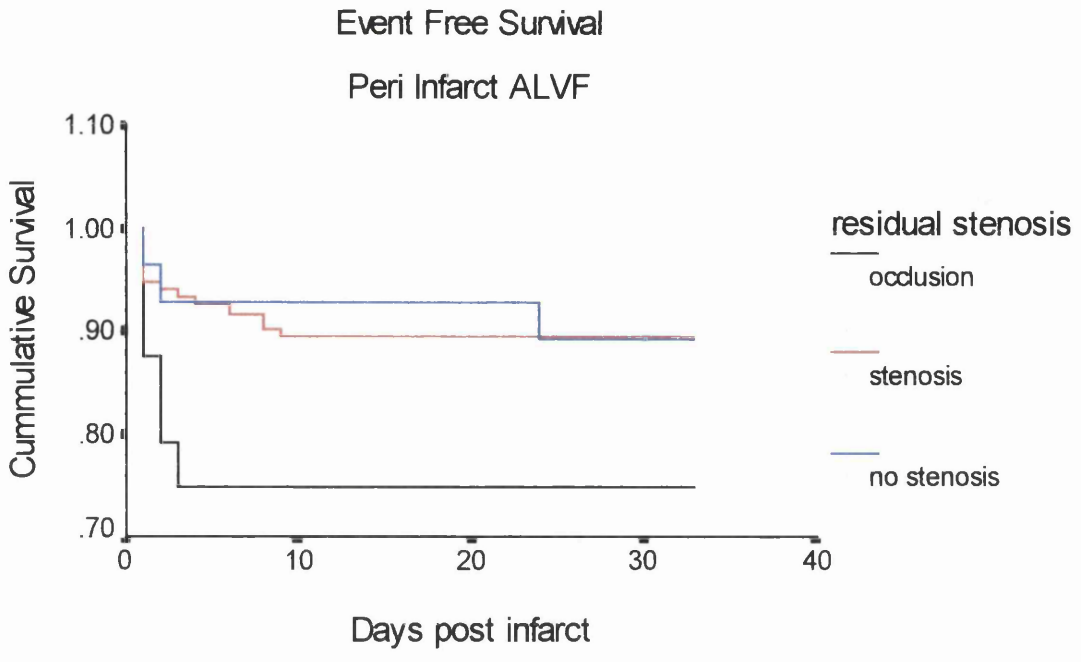

Figure 7-5 Event free survival for peri infarct acute left ventricular failure in relation to residual stenosis.

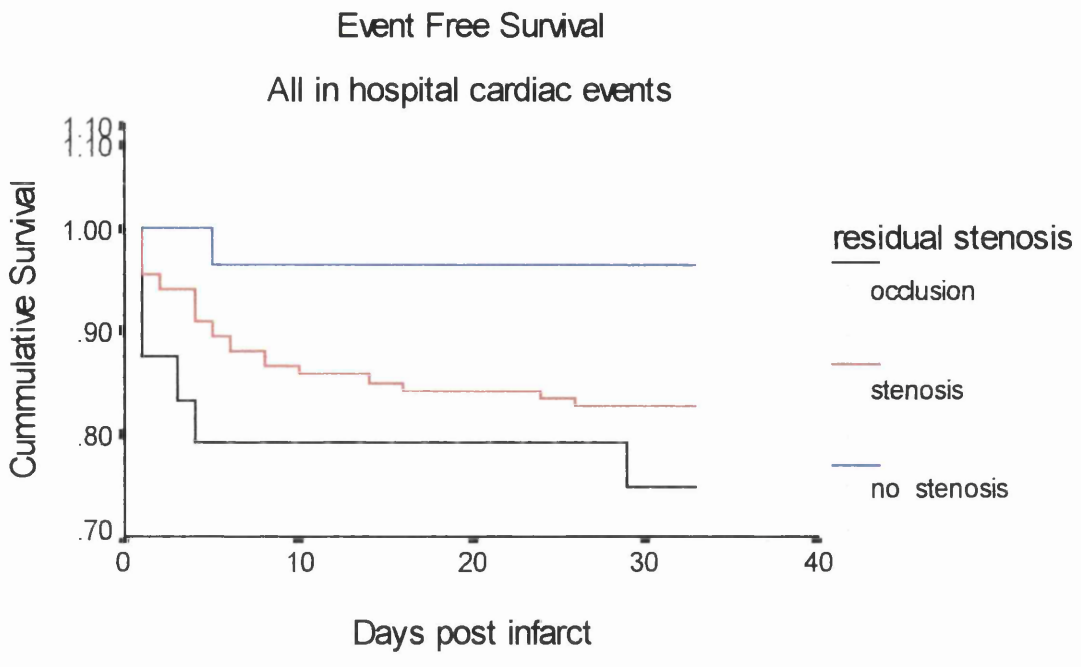

Figure 7-6 Event free survival for all in hospital cardiac events in relation to residual stenosis.

7.2 Residual Stenosis Of The Infarct-Related Artery In Patients With Single Vessel Disease Only

Patients with the infarct related artery as the only affected vessel were analysed as a sub group to determine the effect of an isolated significant residual stenosis (≥ 50%) on the results of exercise testing and clinical outcome. 99 (54%) patients of the 184 undergoing angiography at 24hrs were identified as having single vessel disease. Table 7.7 shows the distribution of patients within each group defined by degree of stenosis. This is illustrated in fig 7.7. As shown above, 70% of patients with single vessel disease had a significant residual stenosis (≥50%).

Infarct-Related Artery	No. of Patients	%
No stenosis	19	19
Stenosis > 50%	70	71
Occluded Vessels	10	10

Table 7.7 Residual Stenosis in Patients with Single Vessel Disease

7.2.1 Symptoms reported during exercise

X^2 analysis was performed to determine whether there was any significant difference between symptoms reported during exercise and the presence of a residual stenosis. This is shown in table 7.8. This is illustrated in fig 7.8..

Symptoms	Stenosis of Infarct Related Artery		
	No Stenosis	Stenosis	Occlusion
Asymptomatic	10	27	2
Symptomatic	8	27	3
(X^2 = 0.409, NS) n=77			
	No Stenosis	Stenosis	Occlusion
Angina	18	48	3
No Angina	0	6	2
(X^2 = 6.826, P < 0.05) n = 77			

Table 7.8 Residual Stenosis in Patients with Single Vessel Disease and All Symptoms during Exercise

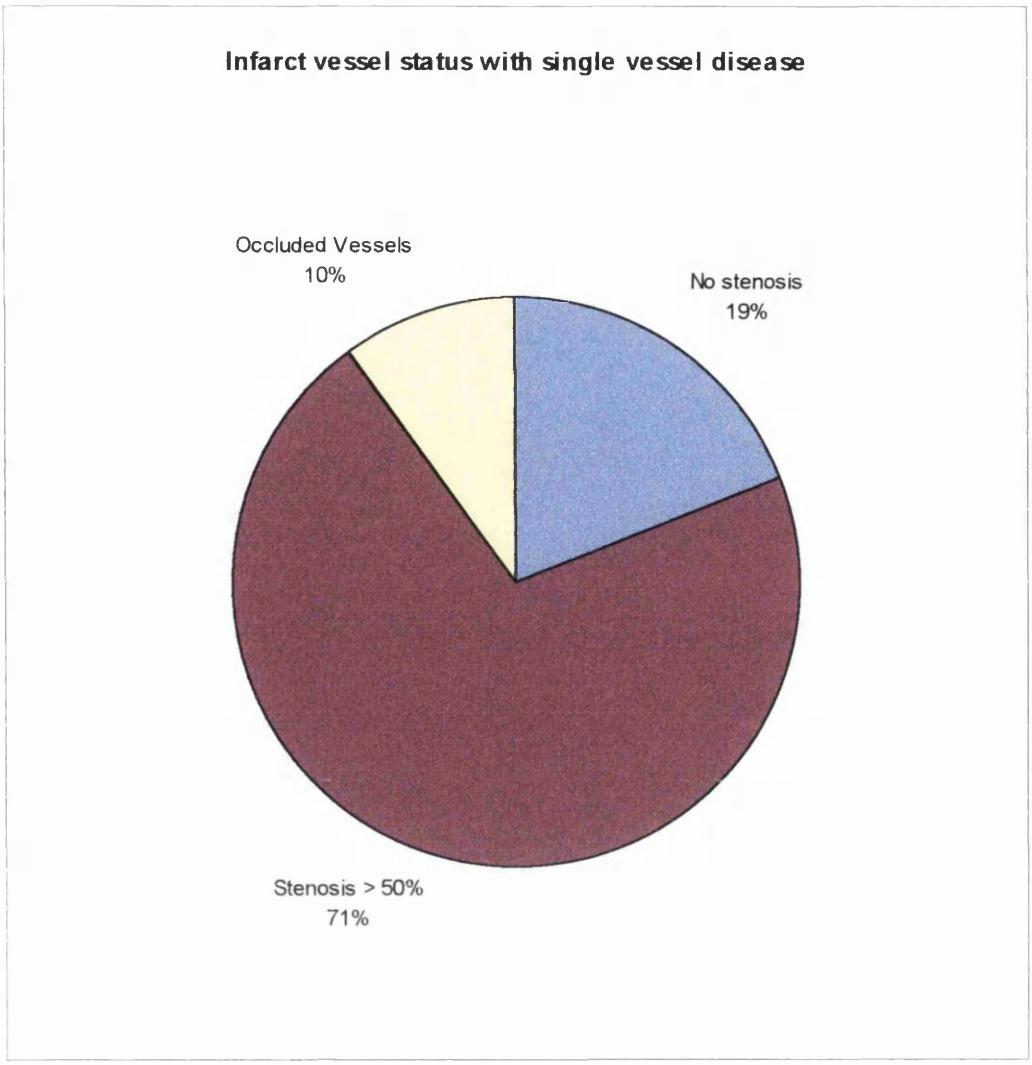

Figure 7-7 Infarct Vessel Status with Single Vessel Disease

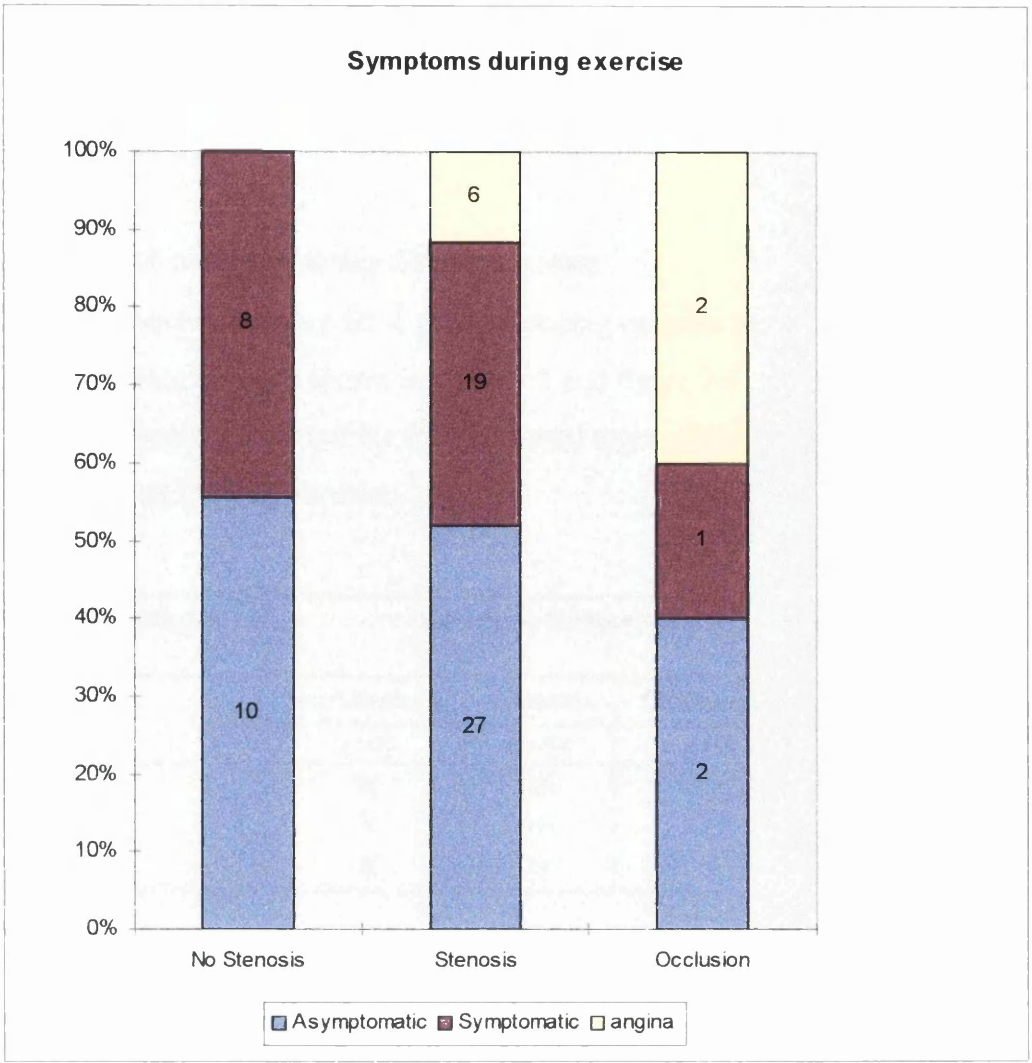

Figure 7-8 Percentage of Patients with Symptoms in relation to residual stenosis with Single Vessel Disease

As shown, patients with no residual stenosis in the infarct-related artery following thrombolysis did not experience angina during exercise. All 18 patients were asymptomatic. 12% of patients with a residual stenosis experienced angina.

7.2.2 ST-T Changes during Exercise testing

The relationship between ST-T changes during exercise testing and stenosis of the infarct related artery is shown in Table 7.9 and figure 7.9. A significant residual stenosis or a complete occlusion of the infarct-related artery did not affect the development of ST-T changes during exercise.

ST-T Changes	Residual Stenosis				
	No Stenosis	Stenosis	Occlusion	X^2	P Value
	n=8	n=54	n=5		
ST ↓	8	16	2	0.284	NS
ST ↑	4	16	2	0.705	NS
T ↑	8	28	2	0.483	NS

Table 7.9 Residual Stenosis in Patients with Single Vessel Disease and ST-T Changes during Exercise

7.2.3 Functional Capacity

Analysis of variance showed no significant relationship between residual stenosis of the infarct-related artery in patients with single vessel disease other exercise variables: total exercise time, metabolic equivalents ,systolic blood pressure response or rate pressure product.

7.2.4 Clinical Outcome

The relationships between residual stenosis in patients with single vessel disease and subsequent cardiac events was assessed by Kaplan Meier event free survival analysis. The results are shown table 7.10 and Table 7.12. The p values for inter group comparisons are shown below each clinical outcome measure. Patients with an occluded artery had a significant increased incidence of ischemic pain post-infarct compared to those patients with no stenosis. (30% v 0%,p=0.059) There was no

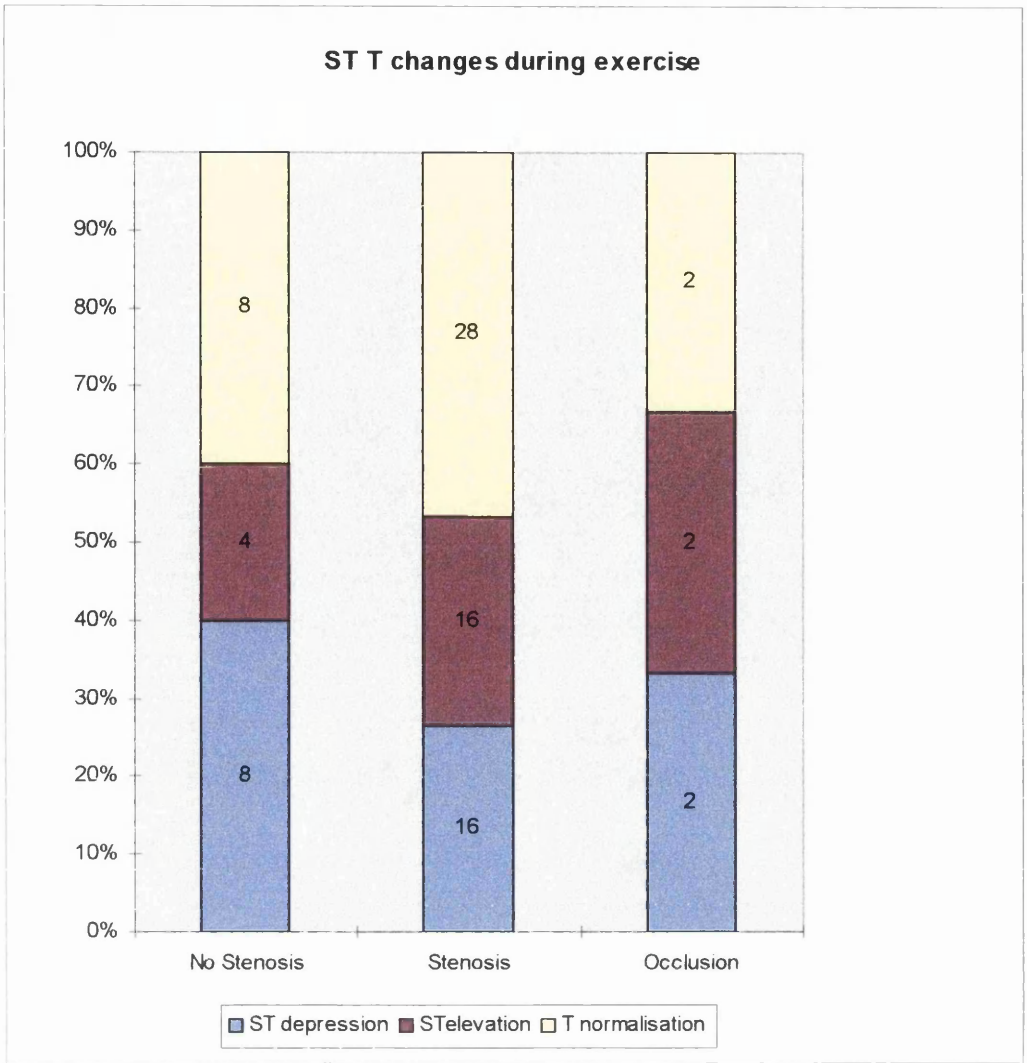

Figure 7-9 Percentage of Patients with Symptoms during Exercise and Stenosis of Infarct Related Aretry with Single Vessel Disease

difference in the incidence of peri-infarct acute left ventricular failure or cardiac ischemic events as an inpatient in relation to residual stenosis with single vessel disease. As shown, the degree of residual stenosis of the infarct-related artery in single vessel disease did not affect the incidence of post-infarct angina, heart failure or cardiac events in out-patient follow up for 5 years. As shown, degree of stenosis did not affect mortality, heart failure or overall cardiac events.

	Residual Stenosis	**No. of Patients**	**No. of Events**	**%**
Ischemic pain	No Stenosis	19	0	0
	Stenosis	70	9	13
	Occlusion	10	3	30
P Values		No Stenosis	Stenosis	
	Stenosis	0.101		
	Occlusion	0.059	0.136	
	Overall			
Acute LVF	No Stenosis	19	2	11
	Stenosis	70	8	11
	Occlusion	10	1	10
P Values		No Stenosis	Stenosis	
	Stenosis	0.855		
	Occlusion	0.159	0.977	
	Overall			
All Cardiac Events	No Stenosis	19	1	5
	Stenosis	70	11	16
	Occlusion	10	3	30
P Values		No Stenosis	Stenosis	
	Stenosis	0.218		
	Occlusion	0.172	0.239	
	Overall			

Table 7.10 Residual Stenosis in Single Vessel Disease and In Hospital Cardiac Events

	Residual Stenosis	No. of Patients	No. of Events	%
Angina	No Stenosis	18	7	39
	Stenosis	70	26	37
	Occlusion	10	4	40
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.6332		
	Occlusion	0.3553	0.633	
	Overall	0.6278		
Heart Failure	No Stenosis	18	3	17
	Stenosis	70	15	21
	Occlusion	10	4	40
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.6836		
	Occlusion	0.3359	0.454	
	Overall	0.6410		
All Cardiac Events	No Stenosis	18	6	33
	Stenosis	70	22	31
	Occlusion	10	4	40
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.6537		
	Occlusion	0.4240	0.227	
	Overall	0.4634		

Table 7.11 Residual Stenosis in Single Vessel Disease and Outpatient Cardiac Events

	Residual Stenosis	No. of Patients	No. of Events	%
Mortality	No Stenosis	18	0	0
	Stenosis	70	3	4
	Occlusion	10	0	0
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.389		
	Occlusion	0.562	0.537	
	Overall	0.567		
Heart Failure	No Stenosis	19	4	21
	Stenosis	70	19	28
	Occlusion	10	4	40
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.813		
	Occlusion	0.567	0.561	
	Overall	0.809		
All cardiac Events	No Stenosis	18	7	33
	Stenosis	70	29	36
	Occlusion	10	4	40
P Values		**No Stenosis**	**Stenosis**	
	Stenosis	0.303		
	Occlusion	0.248	0.544	
	Overall	0.445		

Table 7.12 Residual Stenosis in Single Vessel Disease and Overall Cardiac Events

7.3 The Number Of Vessels Affected By Coronary Artery Disease

Following the visualisation of the infarct-related artery, the non-infarct related artery was outlined to identify additional vessel disease. A stenosis of ≥ 50% was considered significant by the TIMI scoring system of vessel stenosis (appendix V). Table 7.13 show the distribution of 1, 2 and 3 vessel disease in the patients studied. This is illustrated in and fig 7.10. Single vessel disease includes infarct related arteries with no significant residual stenosis. All patients suffered a myocardial infarction and therefore have an underlying atherosclerotic plaque in the infarct related artery which may act as a substrate for further cardiac events.

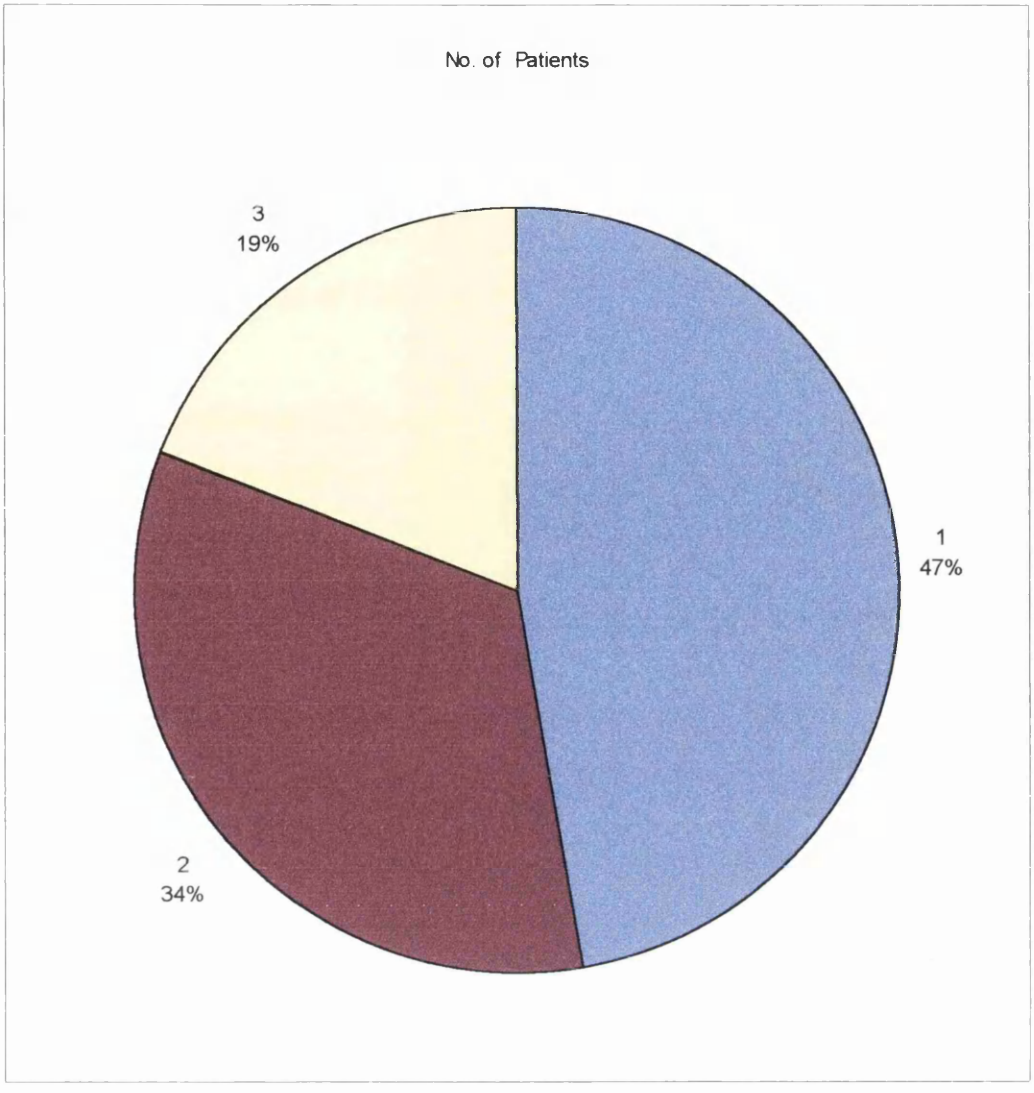

Figure 7-10 Percentage Distribution of Vessel Disease

No. of Affected Vessels	No. of Patients	%
1	94	47
2	67	34
3	38	19
Total	199	

Table 7.13 Percentage of Patients and No of Affected Vessels

As shown approximately 50% of patients had coronary artery disease affecting the infarct-related artery only i.e. single vessel disease.

7.3.1 All symptoms during Exercise

X 2 analysis was performed to see if there was any significant relationship between the number of vessels affected and symptoms reported during exercise. This is shown in table 7.14 and figure 7.11. Patients with single vessel disease had a reduced incidence of angina, but this did not reach statistical significance..

Symptoms	No. of Affected Vessels		
	1	2	3
Asymptomatic	39	28	17
Symptomatic	33	25	9
(X^2 = 1.304, P=NS)			
No Angina	68	43	21
Angina	4	10	5
(X^2 = 6.332, P=NS)			

Table 7.14 No for Affected Vessels and all Symptoms during Exercise Testing

7.3.2 ST-T Changes

Similarly X^2 analysis was used to determine whether ST-T changes during exercise were related to the number of diseased vessels. As shown in Table 7.15 ST segment depression occurred more frequently in patients with 3 vessel disease (X^2 = 11.613, P < 0.05). This is illustrated in and fig 7.12. There was no relationship demonstrated between the number of vessels affected and the development of ST elevation (shown in figure 7.13) or T wave inversion during exercise (shown in figure 7.14).

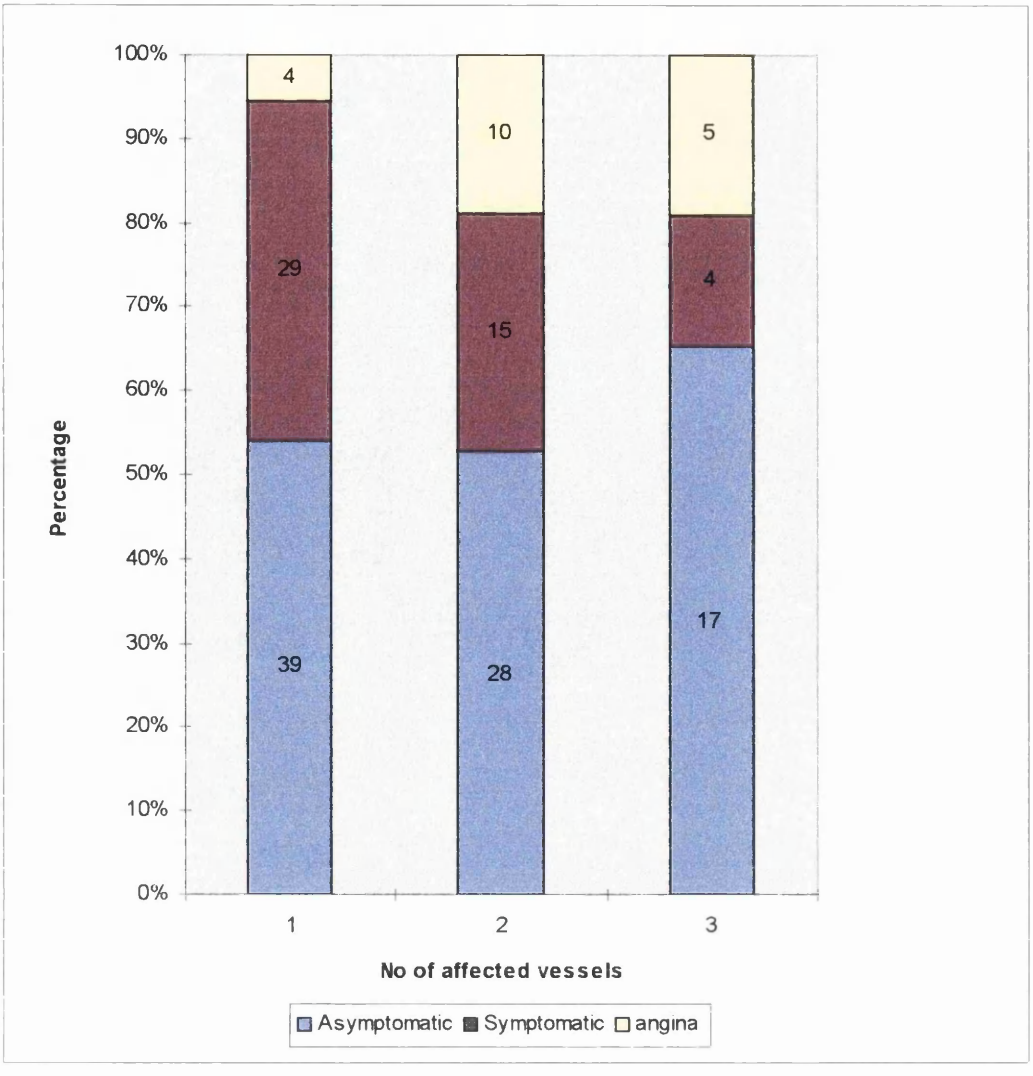

Figure 7-11 No of Affected Vessels and Symptoms during Exercise

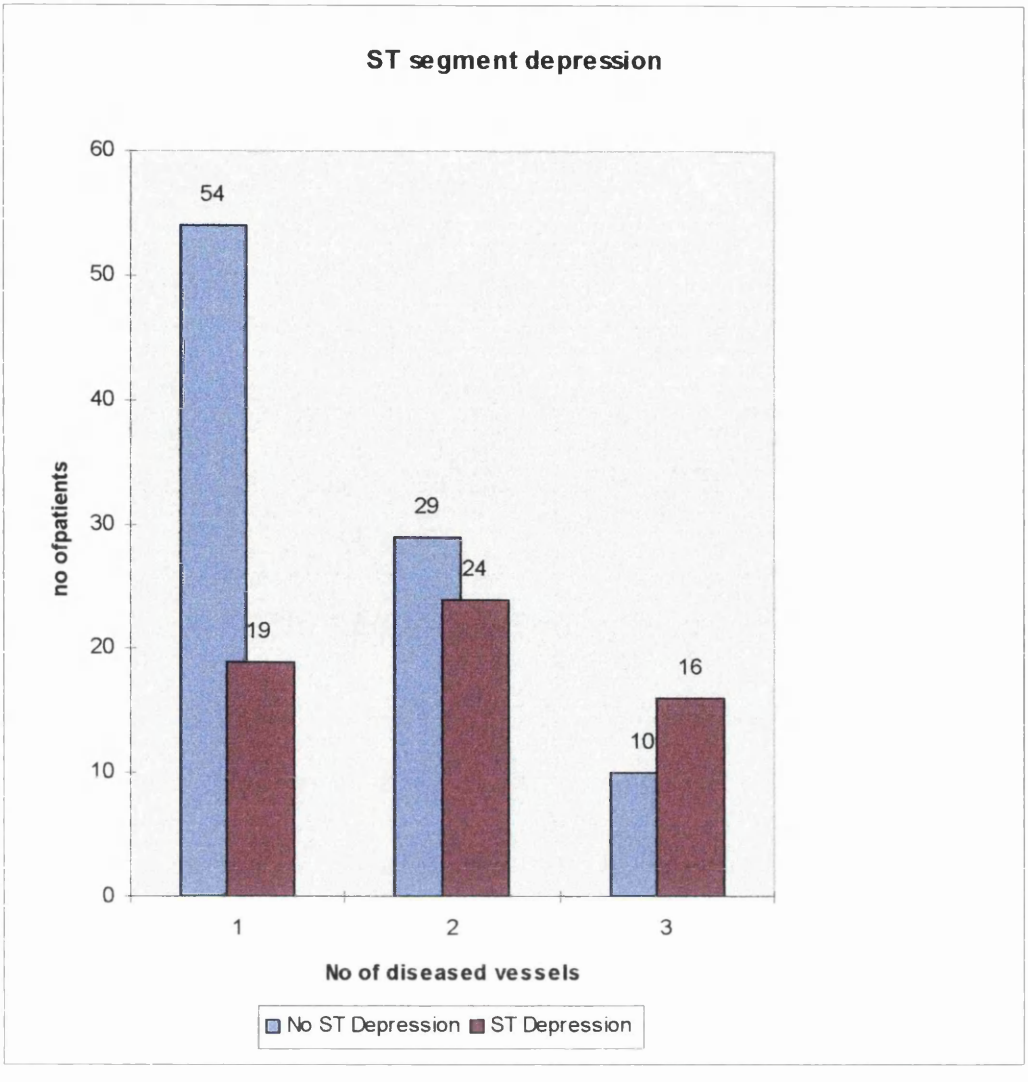

Figure 7-12 No of affected Vessels and Patients with ST Segment Depression during Exercise Testing

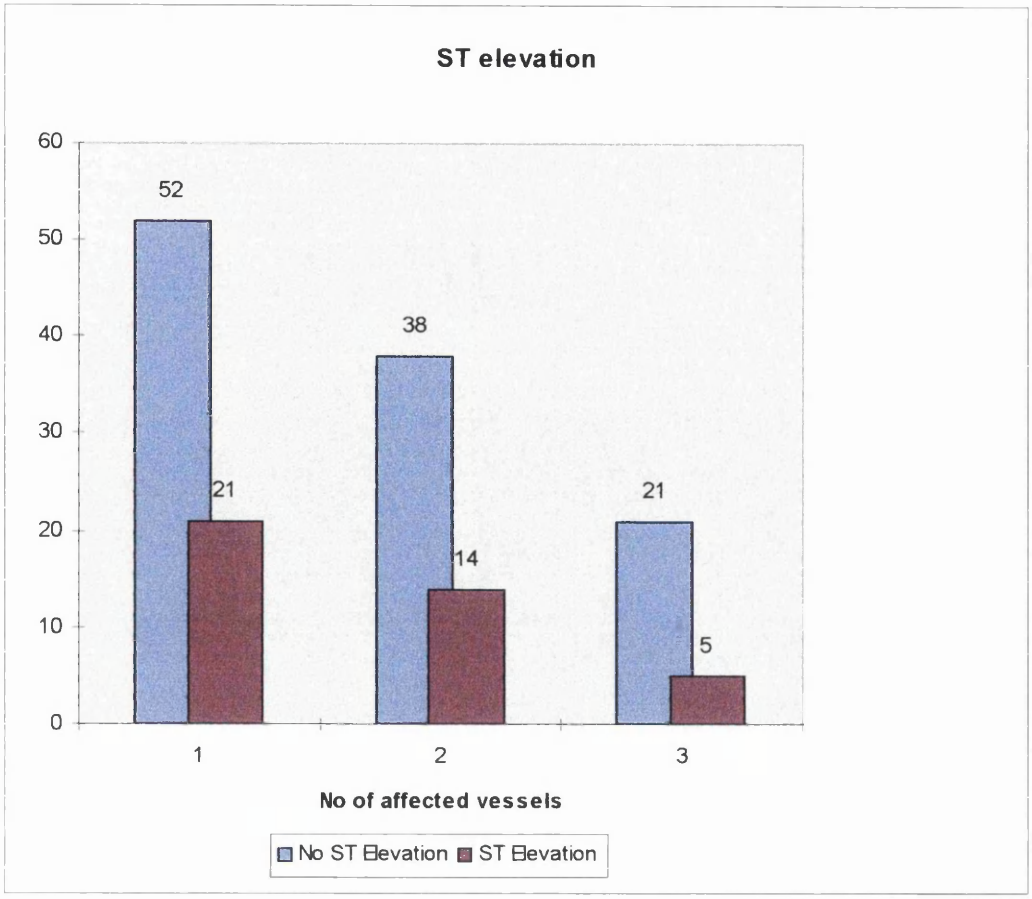

Figure 7-13 No of affected Vessels and Patients with ST Segment Elevation Exercise Testing

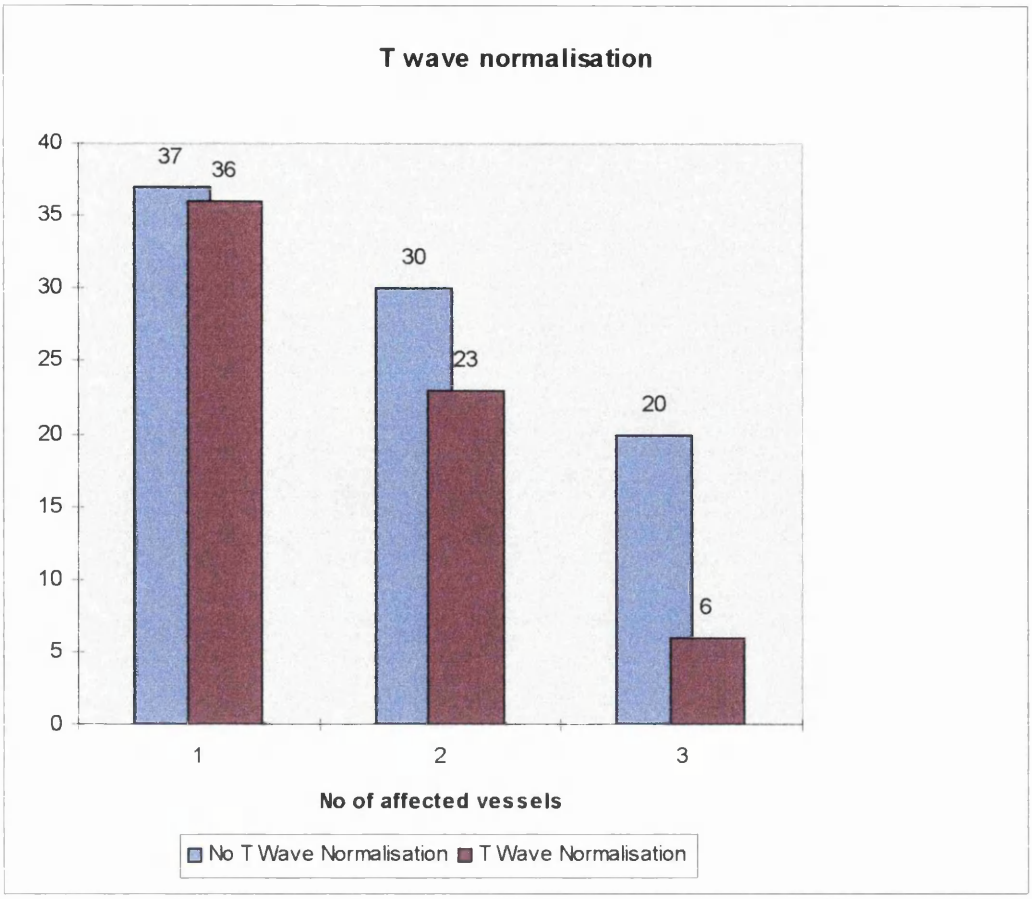

Figure 7-14 No of affected Vessels and Patients with T Wave Normalisation during Exercise Testing

ST-T Changes	No. of Affected Vessels		
	1	2	3
ST Depression			
No ST ↓	54	29	10
ST ↓	19	24	16
(X^2 = 11.613, P < 0.05)			
ST Elevation			
No ST ↑	52	38	21
ST ↑	21	14	5
(X^2 = 0.903, P=NS)			
T Wave Normalisation			
No T Wave ↑	37	30	20
T wave ↑	36	23	6
(X^2 = 5.046, P=NS)			

Table 7.15 No of Affected Vessels and ST-T Changes during Exercise Testing

7.3.3 Functional Capacity

Analysis of variance showed no significant relationship between the number of vessels diseased and other exercise variables: total exercise time, metabolic equivalents ,systolic blood pressure response or rate pressure product.

7.3.4 Clinical Outcome

The effect of number of diseased vessels on in-hospital, outpatient and overall cardiac events was analysed by Kaplan Meier Event free Survival Analysis. This is shown in tables 7.16, 7.17, and 7.18. P values for inter group comparisons are shown below cardiac event data. Vessel disease did not affect the development of post-infarct ischemic pain, peri-infarct acute left ventricular failure or cardiac ischemic events. As shown, patients with 2 vessel disease had a significant increase in the incidence of angina. This was statistically significant compared with single vessel disease. Patients with 2 vessel disease had a greater incidence of heart failure compared to those with 1 vessel disease. However, patients with triple vessel disease showed a significant increase in the total number of cardiac ischemic events compared with single and double vessel disease. The development of heart failure as an outpatient was significantly more common in patients with double vessel disease, which was statistically significant

compared with patients with single vessel disease.(47% v 33% v 30%,p=0.028). As shown, the mortality of patients with triple vessel disease is significantly higher compared with both 1 vessel and 2 vessel disease. The incidence of overall heart failure was higher in patients with 2 vessel disease compared with patients with 1 vessel disease. There was no significant difference in the overall number of cardiac events from day 1 to 5 years in patients with 1,2 or 3 vessel disease.

	No of Affected Vessels	**No of Patients**	**No of Events**	**%**
Ischemic Pain	1	94	11	10
	2	67	8	13
	3	38	2	30
P Values		**2**	**3**	
	1	0.917		
	2	0.265	0.251	
	Overall	0.489		
Acute LVF	1	94	10	10
	2	67	10	15
	3	38	6	16
P Values		**2**	**3**	
	1	0.410		
	2	0.363	0.806	
	Overall	0.583		
All Cardiac Events	1	94	14	15
	2	67	13	19
	3	38	6	16
P Values		**2**	**3**	
	1	0.633		
	2	0.967	0.581	
	Overall	0.837		

Table 7.16 No of Affected Vessels and In Hospital Cardiac Events

	No of Affected Vessels	No. of Patients	No. of Events	%
Angina	1	93	29	31
	2	65	34	52
	3	38	12	32
P Values		**1**	**2**	
	2	**0.001**		
	3	0.225	0.246	
	Overall	0.627		
Heart Failure	1	94	16	17
	2	67	20	30
	3	38	5	13
P Values		**1**	**2**	
	2	**0.024**		
	3	0.813	0.229	
	Overall	0.065		
All Cardiac Events	1	94	31	33
	2	67	20	30
	3	38	18	47
P Values		**1**	**2**	
	2	0.244		
	3	**0.009**	**0.039**	
	Overall	**0.028**		

Table 7.17 No of Affected Vessels and Outpatient Cardiac Events

	Residual Stenosis	No. of Patients	No. of Events	%
Mortality	1	94	5	5
	2	67	3	4
	3	38	8	21
P Values		**1**	**2**	
	2	0.533		
	3	0.001	0.006	
	Overall	0.567		
Heart Failure	1	94	22	23
	2	67	25	37
	3	38	11	30
P Values		**1**	**2**	
	2	0.040		
	3	0.252	0.693	
	Overall	0.117		
All Cardiac Events	1	94	42	45
	2	67	28	43
	3	38	21	57
P Values		**1**	**2**	
	2	0.816		
	3	0.308	0.539	
	Overall	0.308		

Table 7.18 No of Affected Vessels and Overall Cardiac Events

7.4 3 Vessel Coronary Disease v 1,2 Vessel Disease

The effect of three vessel disease was further assessed by comparing it against a combination of 1 and 2 vessel disease. Table 7.19 below shows the distribution of patients with 3 vessel disease. As shown, 16% of patients had 3 vessel disease.

No. of Affected Vessels	No. of Patients	%
1,2	161	81
3	38	16
Total =	199	

Table 7.19 No of Affected Vessels (3VD v 1,2VD)

7.4.1 Symptoms Reported During Exercise

X^2 analysis failed to show any significant difference in the development of symptoms or angina with 3 vessel disease when compared to 1 or 2 vessel disease. This is shown in table 7.20

Symptoms	No. of Affected Vessels	
	1,2	**3**
Asymptomatic	67	17
Symptomatic	59	9
(x^2 = 1.303, P=NS)		
No Angina	112	21
Angina	14	5
(X^2 = 1.299, P=NS)		

Table 7.20 No of Affected Vessels (3VD v 1,2VD) and Symptoms reported during Exercise Testing

7.4.2 ST-T Changes During Exercise

The effect of 3 vessel disease compared to 1,2 vessel disease on ST-T changes occurring during exercise is shown in table 7.21,.22 and 23. As shown, there was a significantly greater incidence of ST segment depression in patients with 3 vessel disease ($P<0.05$). The sensitivity of ST segment depression in the detection of 3 vessel disease was 61.5%, with the specificity of 66%. The predictive accuracy of the positive test was 27% and the predictive accuracy of the negative test was 89%. Therefore, if a patient had a negative exercise test they were very unlikely to have 3 vessel disease. However, if patients had evidence of reversible ischemia on a pre-discharge exercise test, this was not a good predictor of 3 vessel disease. As shown, no relationship exists between ST elevation or T wave normalisation and the incidence of 3 vessel disease.

ST Segment Depression	No. of Affected Vessels	
	1,2	3
No ST ↓	83	10
ST ↓	43	16
(X^2 = 6.819, **P<0.05**)		

Table 7.21 No of Affected Vessels (3VD v 1,2VD) and ST Segment Depression during Exercise Testing

ST Elevation	No. of Affected Vessels	
	1,2	3
No ST ↑	90	21
ST ↑	35	5
(X^2 = 0.850, P=NS)		

Table 7.22 No of Affected Vessels (3VD v 1,2VD) and ST Segment Elevation during Exercise Testing

T Wave Normalisation	No. of Affected Vessels	
	1,2	3
No T wave↑	67	20
T wave ↑	59	6
X^2 = 4.966,P=NS)		

Table 7.23 No of Affected Vessels (3VD v 1,2VD) and T Wave Normalisation during Exercise Testing

7.4.3 Functional Capacity

Analysis of variance showed no significant relationship between the presence of 3 Vessel disease and other exercise variables: total exercise time, metabolic equivalents ,systolic blood pressure response or rate pressure product.

7.4.4 Clinical Outcome

The effect 3 vessel disease on in-hospital, outpatient, and overall cardiac events was determined by Kaplan Meier Event free Survival Analysis and shown in table 7.24, 7.25 and 7.26. 3 vessel disease did not affect the development of post-infarct ischemic pain, peri-infarct acute left ventricular failure or cardiac ischemic events. However, patients

with 3 vessel disease showed a significant increase in the total number of outpatient cardiac ischemic events compared with 1,2 vessel disease (50% v 34%,p=0.004). This is illustrated in fig 7.15. The mortality of patients with 3 vessel disease was increased compared with 1,2 vessel disease (22% v 6%,p=0.0002), illustrated in fig 7.16.

	Vessel Disease	No of Patients	Events	%	P Value
Ischemic Pain	**1,2**	161	19	12	
	3	38	2	5	0.240
Acute LVF	**1,2**	161	20	12	
	3	38	6	16	0.552
All Cardiac Events	**1,2**	161	27	17	
	3	38	6	16	.830

Table 7.24 No of Affected Vessels (3VD v 1,2VD) and In Hospital Cardiac Events

	Vessel Disease	Patients	Events	%	P Value
Angina	**1,2**	158	64	40	
	3	38	12	32	.883
Heart Failure	**1,2**	158	36	22	
	3	38	5	13	.498
All Cardiac Events	**1**	158	54	34	
	3	38	19	50	**.003**

Table 7.25 No of Affected Vessels (3VD v 1,2VD) and Outpatient Cardiac Events

	Vessel Disease	Patients	Events	%	P Value
Mortality	**1,2**	158	8	6	
	3	38	8	22	0.001
Heart Failure	**1,2**	161	47	29	
	3	38	11	30	.793
All Cardiac Events	**1,2**	158	70	45	
	3	38	21	57	.124

Table 7.26 No of Affected Vessels (3VD v 1,2VD) and Overall Cardiac Events

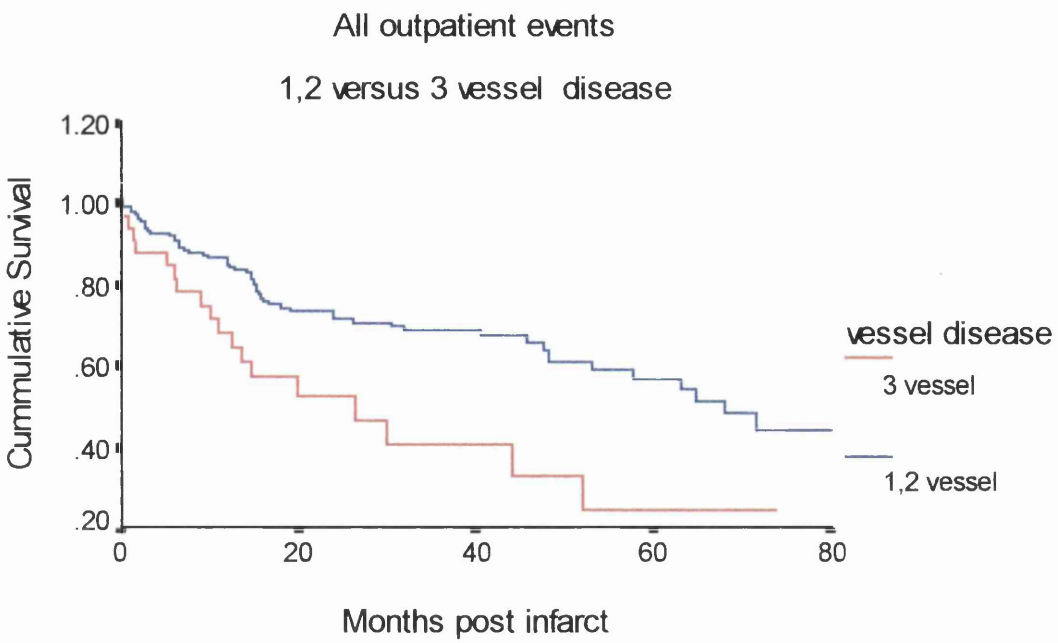

Figure 7-15 No of affected Vessels and Event Free Survival for All Outpatient Cardiac Events

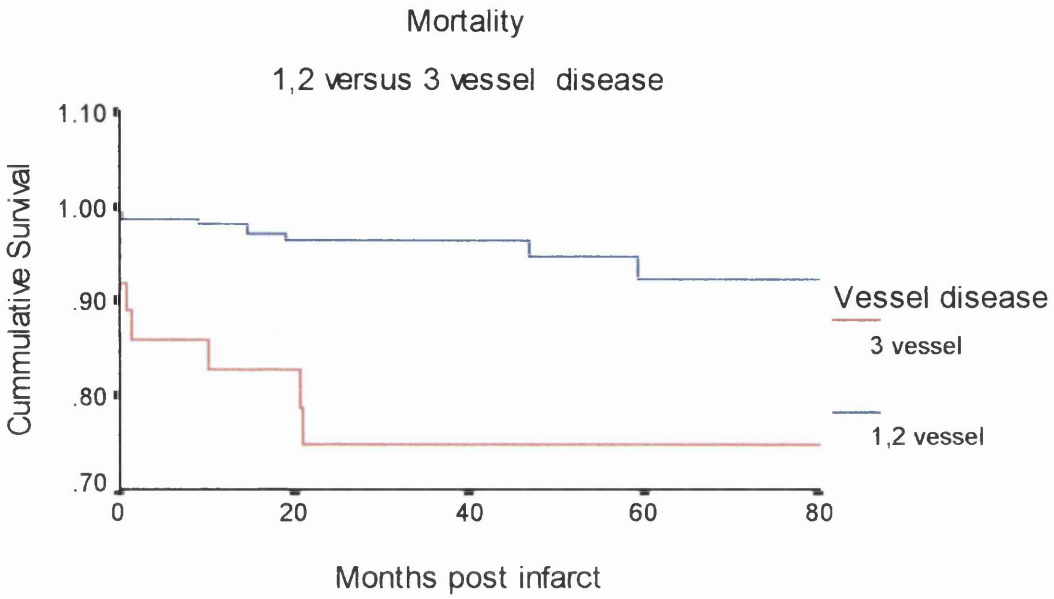

Figure 7-16 No Of Affected Vessels and Event Free Survival for Mortality

8. CLINICAL FOLLOW UP

8.1 Follow up of Patients

Table 8.1 below shows the proportion of patients followed up over the 5 year period. This data represents the last outpatient or in-patient consultation with the cardiology services at the time of retrospective analysis of the case records. The follow up time was then calculated in months for each patient by subtracting the admission date (see appendix VII).This data is shown using event free survival analysis in Figure 8.1.

Time point	No of Patients	%
Admission to CCU	212	100
Discharged from hospital	202	95
1 yr post MI	164	77
3 yrs post MI	93	44
5 yrs post MI	48	23

Table 8.1 Proportion of patients followed up over 5 years

8.2 Mortality

Deaths were recorded as sudden cardiac death or non cardiac. The mortality rates and time point of death are shown over the 5 year follow up period in Table 8.2 below.

Time point	Sudden Cardiac Death	Non Cardiac Death	Total
In Hospital	10	2	12
Discharge to 1 yr follow up	5	0	5
1yr to 5 yr follow up	8	5	13
Total			30

Table 8.1 Mortality over 5 years

10 patients died of cardiovascular causes and 2 further patients died of a cerebrovascular accident during the in hospital phase following myocardial infarction. 77% of patients

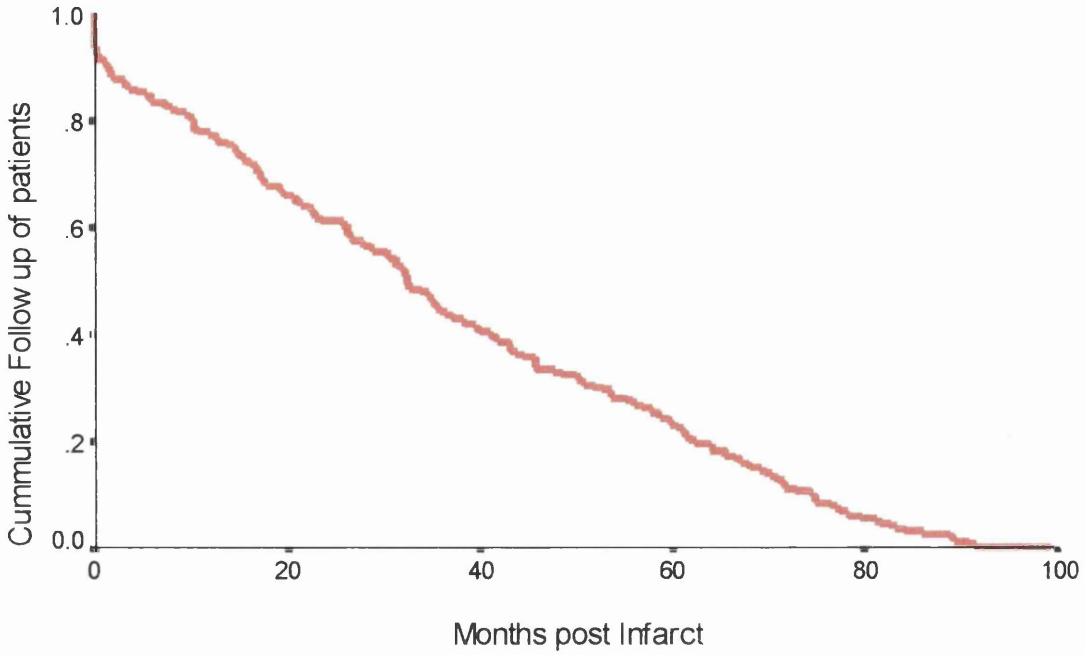

Figure 8.1 Proportion of patients in clinical follow up post myocardial infarction

were followed for 1 yr : this includes in the calculation patients who died during the acute peri infarct period and those who died during the following year. However from the case records 31 patients were either discharged from outpatient clinics or lost to follow up during the first year post infarct.

8.3 In hospital Events

In hospital events are shown in Table 8.3. All primary cardiac events include post infarct ischemic pain, recurrent Myocardial Infarction, PTCA, CABG, and sudden death.

In Hospital Events	Total no of Patients	No in 1st 48hrs (%)
Post Infarct Ischemic Pain	21	9 (43)
Acute Left Ventricular Failure	28	15 (54)
All Cardiac Events	36	17 (47)

Table 8.2 In Hospital Events

8.4 Outpatient Events

All cardiac events from hospital discharge to end of clinical follow up were recorded as outpatient events, shown in table 8.4. Once a primary event had occurred patients were censored within the survival analysis and further events were not recorded. However secondary events such as angina or heart failure and were recorded as cardiac events and analysed separately if they occurred before a primary event.

Outpatient Events	Total no of Patients	No in 1st year (%)
Outpatient Angina	78	56 (71)
Outpatient Heart Failure	43	29 (67)
All Cardiac Events	75	31 (41)

Table 8.3 Outpatient cardiac events

8.5 Overall Cardiac Events

All cardiac events occurring from the admission to CCU with acute myocardial infarction to end of clinical follow up were recorded as overall events, shown in table 8.5

Overall Events	Total no of Patients	No in 1st year (%)
Overall Cardiac Mortality	23	15 (65)
Inpatient mortality		10 (43)
Overall Heart Failure	62	51 (82)
Overall Cardiac Events	96	59 (61)

Table 8.4 Overall Cardiac Events

8.6 Cardiac Events

The total number of recorded cardiac events over the 5 year follow up period are shown in table 8.6. As shown 39% of patients were diagnosed as suffering from angina as an out patient. A relatively high number of patients had post infarct ischemic pain as an inpatient (13%) and overall (24%). This may be explained by the difficulty in establishing this diagnosis from retrospective analysis of the case record and that fact that ECG changes consistent with ischemia were not required to record this as an event. There was a low incidence of revascularisation in this patient group. The low level of a PTCA as an inpatient reflects the fact that Stobhill was not a tertiary referral centre with facilities for angioplasty. All patients requiring angioplasty as an emergency or electively were transferred to Glasgow Royal Infirmary. In addition primary PTCA was not common in management of acute myocardial infarction in Glasgow at that time and in general the patients were managed conservatively. CABG was performed on symptomatic grounds post infarct. Patients with angina or anginal equivalents post infarct were usually reinvestigated by further angiography prior to referral for CABG. Patients were not referred on prognostic grounds for CABG following acute angiography at the time of infarct as the prognosis in this group of patients following myocardial infarction treated with thrombolyisis was not established. In hospital Cardiac death was well recorded in the case record forms. However cardiac death during

the post discharge follow up period was only recorded if the incident was well documented in writing for example in A/E records. If information was lacking regarding the circumstances surrounding the death it was categorised as non cardiac which may have underestimated the number of cardiac deaths

Cardiac Event	Total	%	Inpatient	%
Angina	78	39		
Ischemic pain	51	24	28	13
ALVF	39	18	24	11
CCF	40	18	5	2
Further MI	32	15	7	3
PTCA	10	5	2	< 1
CABG	26	13	0	0
Cardiac Death	23	11	10	5
Non Cardiac Death	7	3	2	< 1

Table 8.5 Cardiac Events: inpatient and overall

8.7 Mulivariate Analysis

A multivariate analysis was carried out using Cox proportional hazard model to determine independent predictors of cardiac events. All clinical, demographic, angiographic and exercise variables which were significant univariates with Kaplan Meier event free survival analysis were entered in a forward conditional stepwise model to determine whether they independently predicted inpatient, outpatient and overall cardiac events; shown in bold below in table 8.7.

In Hospital Events	Independent predictors	Hazard Ratio (95% CI)
Ischemic Pain	none	
Peri infarct ALVF	Reciprocal Depression	2.8(1.1 - 5.5)
All Cardiac Events	none	

Table 8.6 Independent predictors of in hospital events

Outpatient Events s	Independent predictors	Hazard Ratio (95% CI)
Angina	Angina during ETT	2.3 (1.2 - 4.3)
Heart Failure	Anterior Infarct	2.0 (1.1 - 3.7)
All Cardiac Events	none	

Table 8.7 Independent Predictors of outpatient events

Overall Events s	Independent predictors	Hazard Ratio (95% CI)
Mortality	3 Vessel disease	5.8 (1.8 - 18.0)
	Age > Median	3.2 (1.2 - 8.3)
Heart Failure	Anterior Infarct	2.2 (1.2 - 4.1)
All Cardiac Events	none	

Table 8.8 Independent predictors of overall cardiac events

As shown reciprocal depression on the admission ECG was independently predictive of peri infarct acute left ventricular failure. Angina during predischarge ETT was a independent predictor of post infarct angina as an outpatient. Infarct site was predictive of both outpatient heart failure and overall heart failure. Mortality was associated with advanced age and 3 vessel disease.

9. DISCUSSION OF RESULTS

9.1 Introduction

Acute myocardial infarction results from rupture of an atherosclerotic plaque in a coronary arteries with subsequent thrombosis. Total occlusion of the coronary artery without collateral circulation for a sufficient period of time usually results in a Q wave myocardial infarction. The benefits of various thrombolytic agents have now been established in a series of large scale mortality studies (The TIMI Study Group, 1987, AIMS Trial Study Group. 1988; ISIS-2 Collaborative Group. 1988, Wilcox RG et al. 1988; GISSI Working Group 1990; ISIS-3 Collaborative Group. 1992. The Gusto invesigators, 1993). The use of thrombolysis has been shown to reduce mortality by approximately 25% from acute myocardial infarction and improve left ventricular function Thrombolytic agents cause lysis of an occlusive thrombus, with potential salvage of jeopardised myocardium. Animal studies (Reimer KA et al. 1977) showed that reperfusion of a coronary artery within 6 hrs of ligation resulted in significant myocardial salvage. Infarct size and consequent preservation of left ventricular function is dependent on time to reperfusion. This explains why some of the earlier studies of thrombolytic agents which enrolled patients in their study beyond 6 hrs after the onset of symptoms of acute myocardial infarction failed to show true benefits of thrombolysis (Dioguardi N et al 1971, Aber CP et al 1976; Bett JHN et al 1977). Residual left ventricular systolic function following myocardial infarction has been shown to be a potent independent predictor of late survival in the pre-thrombolytic era (Multicenter post infarct research group, 1983; Sanz G et al. 1982). The benefits of thrombolysis in terms of mortality may therefore be due to preservation of left ventricular function following myocardial infarction.

Left ventricular function following thrombolysis will depend upon:

1. Previous myocardial infarction
2. Anatomical location of occlusive thrombus, therefore area of myocardium at jeopardy
3. Time to reperfusion
4. Degree of reperfusion by TIMI score
5. Collateral circulation
6. Ongoing myocardial ischemia.

In the pre-thrombolytic era left ventricular function following a q wave myocardial infarction was dependent upon size of myocardial infarction which in turn was related to site of occlusive thrombus . The area of myocardium at jeopardy became necrotic and healed with scar tissue formation. Inducible reversible ischemia during exercise testing was therefore likely to be related to the extent and nature of coronary artery disease in additional vessels. As described above, thrombolysis potentially alters the coronary anatomy post myocardial infarction. Studies have shown that in 50%-70% of cases there is a significant residual stenosis ($\geq$ 50%) of the infarct related artery following thrombolysis (Sutton JM and Topol EJ, 1991). Therefore if this subtends an area of viable myocardium salvaged by thrombolysis, this may cause recurrent ischemic events(Schaer DH et al. 1987). Exercise testing therefore may induce reversible ischemia in these patients irrespective of additional vessel disease. Residual stenosis of the infarct related artery causing reversible ischemia is therefore an additional reason for left ventricular dysfunction during exercise. Exercise testing, post myocardial infarction has shown in the pre-thrombolytic era to be predictive of future cardiac events (Sullivan ID et al. 1979; Starling MR et al. 1980; ; Davidson MD and DeBusk RF 1980, Jelinek VM et al. 1982; Fioretti P et al. 1986, Vermeulen A, 1988, Belder M et al. 1988, Nielsen JR et al. 1990). Recent studies have reassessed the usefulness of the exercise test following thrombolysis and have shown reduced sensitivity, specificity and predictive accuracy for the exercise test in the prediction of future ischemic events or

cardiac death (Ellis SG et al. 1989; Arnold AER et al. 1993; Stevenson R et al. 1993). However, no study has attempted to correlate the early angiographic assessment (90 min and 24 hrs) of coronary artery patency of the infarct related artery following thrombolysis and additional coronary artery disease, with the results of symptom limited pre-discharge exercise testing and long term clinical follow up. In the TIMI II (The TIMI Study Group, 1993) angiography was performed relatively late between 18 and 48 hrs. Exercise testing in this study was submaximal and used the less common mode of supine bicycle ergometry. More recent studies (The Gusto angiographic invesigators, 1993) have shown the clinical benefits of full patency TIMI score 3 at 90 min post thrombolysis. In addition the follow up period for all these studies has been relatively short and no study to date has identified the predictive value of the exercise following thrombolysis for myocardial infarction over a longer follow up period of 5 years.

9.2 Demographic Characteristics

9.2.1 Age

In the United States 75% of all deaths from coronary artery disease occur in patients > 65 years of age (US Dept of Health and Human Services et al. 1981). Elderly patients have been shown to have a three fold increase in late mortality following myocardial infarction (Norris RM et al. 1974; Henning H et al. 1997). In addition, elderly patients have been shown to have an increased incidence of multivessel disease (Tofler GH et al. 1988) which is obviously one reason for a worse prognosis. The mean age in this study was 55.9$\pm$ 9 yrs with an age range of 31-74 yrs. Patients in the study were obtained from four separate studies of thrombolytic regimes, all of which had an upper age limit of 75 yrs of age for recruitment. Therefore it is not possible to comment on the clinical outcome of patients > 75 yrs of age in this study. Patients who failed to achieve the median workload measured in the metabolic equivalents (5.8 mets) were shown to be statistically significantly older, with a mean age of 57.8 yrs, compared to 52.3 yrs in those patients who an increased exercise capacity. However, there was no significant difference in the age of patients and other exercise variables. The median age in this study was 56 yrs. Patients were divided

into two groups according to the median age. Those patients older than the median age of 56 yrs had a significantly higher incidence of cardiac events as an outpatient ($p=0.054$) and a significantly greater mortality over the 5 yr period ($p=0.023$). There was a trend towards a greater incidence of cardiac events overall in the older patients. There was no significant difference in the age of patients with three vessel disease compared to those with one or two vessel disease, this however can be explained by the relatively young group of patients which were studied .

9.2.2 Sex

Of the 212 patients, 76 % were male and 34% were female. Given the age range of patients was 18-74 yrs this study could potentially include females who are pre-menopausal with a reduced incidence of myocardial infarction. In addition, elderly women above the age of 75 were excluded from this study, where the incidence of myocardial infarction was similar between males and females. For these reasons it is not surprising that the distribution of patients was heavily weighted towards males. Recent multivariate analysis showed no evidence that sex type had any effect on prognosis (Arnold AER et al. 1993). In our study males were more likely to complain of symptoms during exercise testing compared to females (40% v 17%, $p<0.05$). In addition, there was a trend towards males reporting more symptoms of angina compared to females (14% v 3%). Given that the study was heavily weighted towards males, this may represent a type II error. Sex type did not affect other exercise variables or influence the incidence of clinical events during the 5 year follow up study.

9.2.3 Infarct Related Artery

It was possible to find the infarct related artery in 200 of the 212 patients who received thrombolysis for myocardial infarction in this study. In 12 patients the infarct related artery could not be defined. 8 of these patients deteriorated clinically after admission with acute myocardial infarction and the subsequently died. In 4 patients it was not possible to perform angiography due to technical reasons. The right coronary artery was affected in 94

patients (47%), the LAD in 91 patients (45%) and the Circumflex in 15 patients (7%). The low incidence of circumflex artery as the infarct related vessel may be explained by the fact that occlusion of this artery commonly presents as a true posterior infarct. This is diagnosed by ST segment depression and sequential changes of r wave formation in the anteroseptal leads V1-3 of a standard 12 lead ECG. Such ECG changes did not fulfil the criteria for any of the four studies which required frank ST elevation in 2 contiguous leads. With the low number of circumflex occlusions in the study it was decided to compare left anterior descending and right coronary arteries directly and omit circumflex occlusion from the analysis to avoid a type II error. Some studies which identified infarct-related artery post thrombolysis have shown no difference between right coronary artery and left anterior descending artery in the results of exercise testing post myocardial infarction (Sutton JM and Topol EJ, 1991), development of left ventricular dysfunction (Zaret BL et al. 1995) or clinical outcome (Arnold AER et al. 1993). In this study, however, patients with anterior descending artery occlusion were less likely to achieve median workload of 5.8 mets ($p<0.05$). This suggests that LAD occlusion regardless of reperfusion with thrombolysis was associated with more extensive myocardial damage, resulting in reduced left ventricular function and reduced exercise capacity compared to RCA occlusion. Reversible ischemia during exercise teasing defined by ST segment depression was more common in patients who had right coronary artery thrombosis. This was also seen in TIMI II study (The TIMI Study Group, 1993).The explanation for this is not clear but perhaps patients with RCA occlusions having less overall myocardial damage and improved left ventricular function have a greater exercise capacity and are limited during exercise by the effects of reversible ischemia, if there is significant coronary stenosis of the infarct related artery or additional vessel disease, rather than LV dysfunction. There was no significant difference in the incidence of triple vessel disease in patients with LAD v RCA as infarct-related vessel. However, ST segment elevation occurred much more commonly in LAD compared to RCA as infarct-related artery (47% v 8%, $p < 0.001$). ST segment elevation in pre-thrombolytic era has been shown to occur mainly in the presence of anterior infarction and thought to an electrical phenomenon indicative of a wall motion abnormality rather than myocardial ischemia . It has been associated with a lower left ventricular ejection fraction

and a poor prognosis (Sullivan ID et al. 1979). This data suggests that left anterior descending artery occlusion results in more extensive damage to the left ventricle with increased incidence of wall motion abnormality during exercise testing. The development of acute peri-infarct left ventricular failure (p=0.029) and chronic heart failure as an outpatient (p=0.0136) and overall development of heart failure (p=0.003) was strongly associated with LAD as the infarct-related vessel compared to RCA. Studies following thrombolysis have not specifically related heart failure associated with infarct related artery. This is evidence that LAD artery as the infarct-related artery, despite reperfusion therapy with thrombolysis, is associated with reduced left ventricular function and the development of acute left ventricular failure at the time of infarct and congestive cardiac failure over the 5 year follow up period. Patients with LAD compared to RCA occlusions had a greater incidence of T wave normalisation during exercise testing which is likely to represent the same clinical situation as ST elevation.

9.2.4 Site of Infarct

Acute anterior myocardial infarction was compared directly with inferior myocardial infarction. This did include the majority of patients with CX artery occlusions who had infarcts in an the inferior territory. Only 5 patients were defined as having sustained a true lateral infarct with isolated changes in lead I and AVL or V5 and V6 and to avoid a type II error these patients were omitted from the analysis. Patients with anterior myocardial infarction had a reduced exercise capacity measured in metabolic equivalents and increased incidence of an inadequate rise of systolic blood pressure. This implies there is a greater impairment of left ventricular function in anterior myocardial infarction. 96 % of anterior myocardial infarctions, occurred with occlusion of the left anterior descending artery and therefore ST-T changes during exercise were similar to those seen with LAD occlusions. There was a greater incidence of ST segment elevation and T wave normalisation in the infarct site during exercise testing. There was also an increased incidence of ST segment depression with inferior myocardial infarction (similar to right coronary artery occlusion) compared to anterior myocardial infarction. This agrees with the results of TIMI II study

(The TIMI Study Group, 1993) but was contrary to a smaller study which showed an increased incidence of reversible ischemia in patients following anterior infarction following treatment with thrombolysis alone for myocardial infarction (Sutton JM and Topol EJ, 1991). Peri-infarct acute left ventricular failure was significantly more common in patients with anterior myocardial infarction, as was heart failure as an out-patient and overall heart failure Therefore, although this study showed patency rates of 62% (TIMI grade 2,3) at 90 mins, anterior infarct was still a predictor of all heart failure following myocardial infarction which implies more extensive damage to the left ventricle with this diagnosis. Overall mortality from sudden cardiac death was not influenced by site of infarct, however the total number of deaths was small with an overall mortality of 9% from sudden cardiac death in the peri-infarct period and subsequent 5 years of follow up.

9.2.5 Reciprocal depression

Reciprocal ST segment depression is defined as significant ST segment depression in leads relating to the non-infarct site in an ECG with ST segment elevation diagnostic of an acute myocardial infarction. There remains controversy over its significance; whether it represents remote myocardial ischemia due to additional vessel disease (Khaja F et al. 1983) or is merely an electrical phenomenon mirroring ST segment elevation in the infarct site (Akhras F et al. 1985; Jennings K et al. 1983). Reciprocal depression on the original ECG following admission for acute myocardial infarction predicted the development of ST segment depression during exercise testing. There was a reduced incidence of ST segment elevation during exercise in patients with reciprocal depression. This may reflect the fact that reciprocal depression was significantly more common with inferior myocardial infarction ,with associated ST segment depression occurring predominantly in leads I and AVL,which has a reduced incidence of ST elevation. Patients with reciprocal depression on their ECG and a greater incidence of post-infarct ischemic pain and peri-infarct acute left ventricular failure. Reciprocal depression tends to occur with marked ST elevation which represents a larger infarct. Reciprocal depression did not predict outpatient or overall cardiac events. Therefore reciprocal depression on the admission ECG reflects the amount

of myocardium at jeopardy of infarction it does not necessarily equate to the amount of myocardial damage as thrombolysis will achieve patency of the infarct related artery and subsequent salvage. This results in preservation of left ventricular function: which is a major determinant of clinical outcome.

9.2.6 Time to therapy

All patients in this study were treated within 6 hrs of onset of symptoms of acute myocardial infarction.. 3 Groups were identified according to the time of administration of thrombolysis following onset of symptoms: 0-2 hrs, 2-4 hrs and 4-6 hrs. Angina during exercise testing was more common in patients treated within 2 hrs of thrombolysis. This suggests greater salvage of myocardium with early treatment. However, time to treatment did not predict any other variables during exercise testing confirming the results of other studies (Sutton JM and Topol EJ, 1991). Time to treatment does not equal time to reperfusion and combining this time with the results of patency at 90 min and 24 hrs may reflect time to reperfusion more closely. Post-infarct angina as an outpatient was similarly more common in patients treated within 2 hrs with thrombolysis. Multiple comparisons of the three treatment groups were performed and showed the major differences occurred in the development of angina between those treated between 0-2 hrs and 4-6 hrs, and 2-4 hrs and 4-6 hrs. This implies improved benefit to patients treated with thrombolysis within 4 hrs of the onset of symptoms. All cardiac events as an outpatient showed a trend towards an increased incidence in patients treated within 2 hrs of thrombolysis. Multiple comparisons showed this effect was significantly different in those patients treated within 2 hrs compared 2-4 hrs and 4-6 hrs.

9.3 Exercise variables in the prediction of clinical outcome

9.3.1 Exercise Capacity

There was no relationship between exercise capacity measured as total exercise time or metabolic equivalent and cardiac events during the follow up period. Several studies in the pre-thrombolytic era (Davidson MD and DeBusk RF, 1980; Jennings K et al. 1984; Weld

FM et al. 1997; Valesco JA et al. 1981) showed that reduced exercise capacity caused by 3 vessel disease or impaired LV function, was predictive of an adverse outcome. A study in the post-thrombolytic era, showed that failure to achieve a median workload of 7 mets was predictive of recurrent cardiac events. However, it had a poor positive predictive accuracy of 21%. This reflects improved mortality with thrombolysis and the other potential reasons for reduced exercise capacity in the post thrombolytic era which do not necessarily have an adverse prognosis.

9.3.2 Systolic Blood Pressure

Prior to widespread use of thrombolysis, an abnormal systolic blood pressure response during exercise testing post myocardial was shown to be predictive of future cardiac events. An increased mortality was associated with failure of systolic blood pressure to rise by 30 mmHg during exercise testing (Nielsen JR et al. 1990; Jennings K et al. 1984) or failure to reach a peak systolic blood pressure > 140 mmHg (Fioretti P et al. 1984; Starling MR et al. 1980). In a study in 1993 it was shown that failure of systolic blood pressure to increase by > 30 mmHg was a weak predictor of mortality after thrombolysis for acute myocardial infarction within the 1st year, with a relative risk of 2.9 (Arnold AER et al. 1993). In this study accurate blood pressure data was recorded by manual measurement in only 48 of the 156 patients who were exercised. Total number of events in each group were small and this may have caused a type II error in this analysis.

9.3.3 Rate Pressure Product

Rate pressure product in the pre-thrombolysis rate pressure product was shown in one study (Saunamaki KI and Anderson JD, 1982) to be a predictor of cardiac death over a mean follow up period of 5.7 yrs. Median rate pressure product in our study was 5800. Failure to achieve this median value was not predictive of outpatient clinical events but was subject to the same potential problems with type II error as systolic blood pressure data. In addition patients on B blockers would have a reduced rate pressure product and as no attempt was made to alter prescribed treatment prior to the exercise test patients these may have been

classified in the group who failed to achieve the median rate pressure product without any added risk.

9.3.4 ST segment depression

In the pre thrombolytic era approximately 30% of patients recovering from a myocardial infarction had ST segment depression during predischarge exercise testing (Williams WL et al. 1984). In 1979 Theroux et al in an influential study of 210 patients with uncomplicated myocardial infarction showed that ST segment depression of ≥ 1 mm in a low level exercise test performed at a mean of 11 days post-infarct was highly predictive of mortality in the 1st year. The strength of this study was on lack of intervention with medical therapy or revascularisation during the follow up year. Any intervention was performed on the basis of clinical symptoms and not the results of exercise testing. However, there were very small numbers of events in both groups. Other studies supported this result (Davidson MD and DeBusk RF, 1980; Belder M et al. 1988; Kentala E, 1976). However, Sanz G et al. In 1982 showed that ST segment depression was not predictive of clinical outcome in 259 males recovering from myocardial infarction. Further studies (Nielsen JR et al. 1990; Jennings K et al. 1984; ESC Working Group on Exercise Physiology Pathophysiology and Electrocardiography, 1993) also identified reversible ischemia as a predictor of adverse prognosis. In a meta-analysis of 12 studies published in (Arnold AER et al. 1993), there was a increase in sudden death or reinfarction with ST segment depression of ≥ 1 mm during exercise testing post myocardial infarction with an overall odds ratio of 1.9. The positive predictive accuracy of ST segment depression in identifying all cardiac events was 80% and mortality alone was 90% in the study by Theroux in 1979. Since the widespread use of thrombolysis the predictive value of exercise testing has been re-assessed (Stevenson R et al. 1993). In this study there was reduced sensitivity, specificity and positive predictive accuracy compared to the previous studies in the pre-thrombolytic era. However, there was retained negative predictive accuracy. Therefore a normal exercise test following myocardial infarction treated by thrombolysis indicates a good prognosis, and these patients can potentially be discharged from clinical follow up. However, an abnormal exercise test

is no longer able to clearly stratify patients into those at high risk of further current ischemic events. Before the advent of thrombolysis, the Q wave myocardial infarction caused a fixed amount of myocardial damage which healed with scar tissue formation. Subsequent recurrent ischemic events including reversible ischemia during exercise testing therefore reflected the presence of additional vessel disease which carries an adverse clinical prognosis. Thrombolysis alters coronary artery anatomy post-infarct by achieving reperfusion of an infarct-related artery in at least 60% of patients and resulting in a residual stenosis in about 70% of patients (Sutton and Topol 1991) which supplies an area of myocardium with variable viability. This is, therefore, an additional reason for recurrent ischemic events and reversible ischemia during exercising testing post-myocardial infarction. Therefore, there are additional reasons why a patient might develop ST segment depression during exercise testing. They do not however carry the same adverse prognosis, especially in patients with single vessel disease. Thrombolysis reduces mortality in myocardial infarction and preserves left ventricular function. By Baye's theorem the positive predictive accuracy of any test performed to identify adverse outcome will be reduced as a result improved mortality post-myocardial infarction with thrombolysis (Northridge DB and Hall RJC, 1997)

9.3.5 ST-Segment Elevation:

ST segment elevation during exercise testing following myocardial infarction is more common in patients with anterior-myocardial infarction. It usually occurs in the infarct site which often has residual ST elevation following myocardial infarction. Some studies have shown ST elevation during exercising testing to be predictive of outcome (Belder M et al. 1988; Sullivan ID et al. 1979) but there remains controversy as to its the significance (Nielsen JR et al. 1990; Fioretti P et al. 1986). It is likely that ST segment elevation during exercise represents a wall motion abnormality of the infarct site rather than reversible ischemia. This has a complex relationship with exercise ejection fraction (Sanz G et al. 1982) and subsequent functional capacity. The TIMI II study showed that ST Elevation during post infarct exercise testing occurred predominantly in the infarct site and these

patients had a lower resting ejection fraction and increased 1 yr mortality (The TIMI Study Group, 1993). .In this present study of 212 patients treated with thrombolysis ,ST segment elevation. during exercise testing occurred frequently in the infarct site as defined by the admission ECG, but failed to predict clinical outcome in keeping with recent studies in the post thrombolysis era (Stevenson R et al. 1993). Normalisation of inverted T-wave during exercise testing post-myocardial infarction has not been extensively investigated in previous studies. This occurred exclusively at the site of infarction. However, this is not surprising as T wave inversion occurs as part of sequential ECG changes in the site of myocardial infarction and is not normally present in a non-infarct site. T-wave normalisation did not predict clinical outcome and should be considered as a benign electrical phenomenon.

9.3.6 ST-Segment Depression with low workload

In an attempt to improve the predictive value of ST-segment depression this variable was to combined this variable with failure to achieve a median workload of 5.8 mets and the combination used to reassess predictive value of the exercise test. ST segment depression at a low workload has been shown to improve the predictive value of the predischarge exercise test (Stevenson R et al. 1993) following thrombolysis but this present study failed to confirm these results. Perhaps the median workload of 5.8 mets was not representative of a significant reduction in exercise capacity .In clinical management of patients with angina, age predicted exercise time, calculated from a nomogram, is used to assess a reduction in functional capacity. This criterion has not been applied to patients post myocardial infarction in the predischarge exercise test which commonly uses modified protocols.

9.3.7 Failure to Undergo Exercise Testing

Several studies have shown patients failing to undergo an exercise test following a myocardial infarction had a worse prognosis (Gissi Working group, 1993; The TIMI Study Group, 1993; Peart I et al. 1989).This implies that this group of patients had complicated

myocardial infarctions, other physical disabilities or ongoing disease processes which rendered them unsuitable for exercise testing. Fourteen patients who died during the in-patient period were ineligible to perform pre-discharge exercise testing and therefore not included in the results as this would lead to significant bias. Twenty-six per cent of patients eligible to have exercise testing did not do so. In this study, following acute admission to the Coronary Care Unit and subsequent angiography, the patients were then transferred to a general medical ward, usually but not always, under the care of one of the three Consultant Cardiologists. Occasionally, patients were transferred under the care of general physicians who happened to be on call for emergency referrals on the day of the patient's admission to Coronary Care. As the analysis of clinical events was retrospective, it was not possible to define why 26% of patients did not undergo exercise testing as the reasons were not stated in the patients' case records. Therefore, within this group of patients, although the majority were not physically fit to undergo exercise testing at the time of discharge there may also be a subgroup of patients who were fit to undergo exercise testing but did not do so because of the management strategy of the attending physician. Failure to undergo predischarge exercise testing did not predict any cardiac events during follow-up. Given that a proportion of these patients were suffering from additional chronic diseases, it was reasonable to include deaths from other causes. 18% of patients who did not undergo predischarge exercise testing died from all causes over the 5-years of out-patient follow-up. This was statistically significant compared to those who completed an exercise test and probably reflects an increased incidence of cardiac complications post myocardial infarct and comorbidity in the non exercise test group.

9.3.8 Symptoms during exercise testing

In this study, patients underwent a symptom limited exercise test and were only stopped by the attending physician if they reached maximum heart rate, developed a significant arrhythmia, ST-segment depression of ≥3mm or systolic blood pressure fell by ≥ 20mmHg.. Patients reported a variety of symptoms but 70 patients,(45%) were asymptomatic during exercise testing and were stopped electively by attending physicians for the reasons

outlined above. Combined symptoms during predischarge exercise testing did not predict clinical outcome. This is probably due to the non specific nature of the symptoms reported during exercise.

9.3.9 Angina:

Only 19 patients [12%] experienced angina during the predischarge exercise test. In the pre thrombolytic era approximately 20% of patients recovering from a myocardial infarction developed angina during predischarge exercise testing(Williams WL et al. 1984, Theroux et al. 1979 showed that angina occurring during the predischarge exercise test predicted development of post-infarct angina as an outpatient. Furthermore, the development of angina during exercise testing was not predictive of clinical cardiac events. In this present study patients with angina during post-infarct exercise testing were more likely to develop symptoms of angina during daily activity as an outpatient (63% v 37% p=0.007)..A reanalyses of this data from Theroux presented on page 33 of the introduction shows that angina was predictive of all coronary events if post-infarct angina itself was removed as an event but was not predictive of mortality. The predictive accuracy of the positive test, namely angina during exercise testing, was poor for both all cardiac events 31 % and mortality 16%. Other studies report angina pectoris as predictive of future coronary artery bypass surgery (ESC Working Group on Exercise Physiology Pathophysiology and Electrocardiography, 1993),recurrent myocardial infarction or sudden cardiac death (Peart I et al. 1989; Davidson MD and DeBusk RF, 1980). The number of patients undergoing coronary artery bypass surgery over a 5 year period was very small in the study by Theroux P et al. 1979 and was not considered as a cardiac event in isolation.

Patients with significant angina post infarct may be considered for CABG on clinical grounds. Of the 62 Patients with angina as an outpatient over the 5 year follow up period 18 had CABG performed. This would depend on severity of symptoms , suitability of coronary anatomy and comorbidity. 8 patients without symptoms of angina had CABG performed on prognostic grounds following repeat angiography. In general patients were not referred

for CABG on the basis of angiography at 90 min and 24 hrs post thrombolysis as the prognosis on the basis of coronary anatomy was unknown. Patients were usually reinvestigated by coronary angiography on clinical grounds after recovery from the infarct.

9.4 Coronary patency:

Coronary artery patency of the infarct-related vessel in this study was assessed by TIMI scoring of coronary angiogram performed at 90 minutes and 24-hours following thrombolysis for acute myocardial infarction.

9.4.1 TIMI score at 90 mins:

194 of the 212 patients underwent angiography. At 90 minutes, 8 patients were clinically too unwell to undergo coronary angiographic assessment. The TIMI score at 90 minutes did not predict any symptoms or complaints of angina during exercise testing. Similarly, there was no relationship between a TIMI score at 90 minutes and ST-T changes during exercise and measurements of functional capacity.

9.4.2 TIMI score at 24-hours:

187 out of 212 patients underwent angiography 24-hours following thrombolysis. Coronary angiography was contraindicated because of the significant deterioration in the clinical condition of 11 patients ,8 patients died during the first 24-hours. It was not possible to perform repeat angiography in 7 patients for technical reasons, involving the arterial sheath which had been left *in situ* in the right femoral artery. At 24-hours, 58% of patients had TIMI -grade 3 flow in infarct-related vessel, 12% of patients had no established flow [TIMI grade 0]. There was no relationship between TIMI score at 24-hours and symptoms during exercise testing, ST-segment changes or measurements of functional capacity. The coronary patency was further defined by combining TIMI score 0 and 1 as non-patent arteries and TIMI score of 2 and 3 as patent arteries at 90 minutes and 24-hours (62% of patients and 83% of patients had patent vessels at 90 minutes and 24-hours, respectively). Patency did not appear to affect the results of the exercise testing in terms of symptoms,

ST-T change of measurements of functional capacity. Thrombolysis has been shown to lead to an increased incidence of recurrent ischemic events (Schaer DH et al. 1987) post-infarct defined as

1. Spontaneous angina at rest or during ward ambulation,
2. Provokable angina during predischarge exercise test
3. Reinfarction

Patients who reperfused with thrombolysis were more likely to experience recurrent ischemic events as were those with sub-total occlusion of the infarct-related vessel identified with pre-treatment coronary angiography. This early study, however, did not use TIMI scoring system to quantify patency of the infarct-related vessel and, therefore, treated reperfusion qualitatively as and all or nothing phenomenon. Only symptoms of angina during exercise testing were recorded no other exercise variables were considered. Patients treated with thrombolysis were shown to have no increased incidence of positive exercise test defined as typical angina or ST-segment depression versus placebo (Hamouratidis N et al. 1991). Patients with recannalised arteries had increased incidence of normal exercise tests. However, in this study angiography was performed 22.9 days following thrombolysis when infarct artery remodelling and time-dependent reperfusion without myocardial salvage may have occurred. Van Der Wall EE et al 1997 performed an angiographic assessment of patency at 2-hours following streptokinase and showed no relationship between coronary patency defined as TIMI grade 2 and 3 and non patent vessels in a the number of persistent or reversible perfusion defects present on thallium scanning. The authors did not attempt to relate patency or other variables during exercise testing. Coronary patency *per se* may not guarantee significant salvage of myocardium. Reperfusion following thrombolysis may occur at various time points post therapy resulting in a variable amount of residual .viable myocardium in the region supplied by the infarct-related artery. Other factors, such as a collateral circulation, the site of coronary occlusion

or duration of occlusion, may influence the quantity of myocardium salvaged. In this present study failure to achieve coronary patency with thrombolysis [TIMI score 0 and 1] at 90 minutes was shown to predict post-infarct ischemic pain. This includes 6 patients with coronary reocclusion between 90 minutes and 24-hours, therefore, it is not surprising that post-infarct ischemic pain was more common in this group. Failure to achieve coronary patency at 24-hours gave a trend towards increased incidence of peri infarct acute left ventricular failure. Non-patency at 90 min was predictive of chronic heart failure as an out-patient. There was an increased incidence of overall heart failure in those patients with non patent arteries at 90 minutes. This is supported by recent evidence from the GUSTO study in 1993 which showed overall patency: TIMI grades 2 and 3 combined and full patency TIMI grade 3 resulted in a reduced incidence of left ventricular dysfunction assessed by left ventricular angiography and improved mortality at 30-days..

9.4.3 Effect of full Patency:

The effect of full patency TIMI grade 3 on exercise variables following thrombolysis were further assessed by comparing TIMI score 3 against TIMI score 0, 1 and 2 at 90 minutes and 24-hours with thrombolysis. 36% and 58% of patients were assessed as TIMI grade 3 at 90 minutes and 24-hours, respectively. There was no relationship between TIMI grade 3 and development of symptoms, ST-T changes or measurements of functional capacity during exercise testing. However, TIMI grade 3 was shown to favourably improve patient prognosis. The development of peri-infarct acute left ventricular failure, chronic heart failure as an out-patient and heart failure overall, were all significantly reduced in patients with TIMI grade 3 patency post-thrombolysis. Sudden cardiac events were also significantly reduced with TIMI grade 3. This supports the data from GUSTO study 1993 which compared TIMI grade 3 versus TIMI grade 0,1,2 and showed a significant reduction in the incidence of left ventricular dysfunction and improved mortality. Although factors other than patency will affect left ventricular function and the development of heart failure in the peri-infarct and post-infarct periods, achieving early patency is a definite benefit to

prognosis.

9.4.4 Time to Patency:

By combining TIMI scores of the angiographic assessments at 90 minutes and 24-hours, it was possible to define four patency groups: early patency [EP], late patency[LP] non-patency [NP] and Reocclusion[R].Only six patients [3%] had coronary reocclusions at 24-hours following thrombolysis, 60% of patients had early patency, 24% had late patency and 13% were non-patent. To avoid a type II error reocclusion with such small numbers were not included in further analysis. Time to patency had no effect on symptoms during exercise testing, ST-T change or measurements of functional capacity. Post infarct ischemic pain occurred more frequently in patients with non-patent vessels, i.e. TIMI grade 0,1 at 90 minutes and 24-hours. It is possible that reperfusion had occurred in these patients between 90 minutes and 24-hours but at the time of the 24-hour angiogram, the vessel was again non-patent. Therefore reperfusion and reocclusion was associated with anginal pain. Acute left ventricular failure in the peri-infarct period, chronic heart failure as an out-patient and combination of both [overall heart failure] were significantly more common in patients with non-patent arteries compared to early and late patency. No previous studies have used TIMI scoring in this way to predict results of exercise testing and clinical outcome over 5 years.

9.5 Residual Stenosis of the Infarct-Related Artery:

In this study, residual stenosis of the infarct-related artery was considered both in single vessel disease and in the presence of additional vessel disease. The TIMI scoring system of coronary artery stenosis was used and which defines a significant stenosis as being $\geq$ 50% narrowing of the luminal diameter of the coronary artery. Patients with no additional vessel disease were considered as having the single vessel disease and further analysed to determine the effect of significant residual stenosis. Coronary artery anatomy, following the 24-hour angiogram, was used to predict the results of exercise testing and clinical outcome because this was the closest angiographic assessment in time to the exercise test.

72 % of patients had a significant stenosis of the infarct-related artery with or without multivessel disease and in 13% of patients the infarct-related artery was occluded. 147 of 186 patients who had coronary artery anatomy defined at 24-hour angiogram were exercised prior to discharge. No relationship was noted between residual stenosis of the infarct-related artery and development symptoms or ST-segment changes or functional capacity during predischarge exercise testing .Therefore, although a residual stenosis of the infarct related artery was present in over 70% of patients it also requires viable myocardium to result in reversible ischemia during the exercise test. No assessment of myocardial function was made in this study.

Ischemic pain post-infarct occurred in 5 of the 24 patients with occluded vessels and was significantly more common when compared to those with no residual stenosis. Coronary occlusion occurring between 90 minutes and 24-hours may result from reocclusion of a previously patent vessel or persistent occlusion of arteries with TIMI grade 0 or 1 at 90 minutes. Angiographic assessment has been made at two points in time and cannot, therefore, account for fluctuating patency between these two time-points which may have resulted in early post-infarct ischemic pain. Post-infarct acute left ventricular failure was more common in patients with occluded vessels. The number of events in the occlusion group compared to the no stenosis and stenosis group were relatively small which may have affected the results in multiple group comparisons. In an occluded vessel at 24-hours, unless there is a significant collateral circulation, there will be significant myocardial necrosis of the area supplied by that vessel which will result in a variable degree of left ventricular dysfunction, dependent on the site of occlusion. It is, therefore, not surprising that patients with persistent coronary occlusion, post-thrombolysis are more likely to develop peri infarct left ventricular failure. However no assessment of site of occlusion was made in this study. All cardiac ischemic events were similarly more common in patients with occluded vessels. There is no significant difference in the occurrence of outpatient cardiac events or overall cardiac events with residual stenosis. Patients with no residual stenosis in the infarct related artery or any additional vessel disease were still categorised as

single vessel disease .. The concept of 0 vessel disease used by some authors was not applied to this data. Patients with a residual stenosis of ≤ 50% still have an underlying atheroscleortic plaque and therefore the potential for recurrent ischemic events. 99 [54%] of patients had single vessel disease. Similarly, 70% of these patients had a significant stenosis and 10% had occluded vessels. The residual stenosis in the patients with single vessel disease did not predict the results of exercise testing in terms of symptoms and ST-segment changes or functional capacity. Patients with occluded vessels, however, had a significant increase in pain post-infarct but not left ventricular failure following infarction or all cardiac ischemic events. Out-patient and overall cardiac events were not predicted in the presence of residual stenosis of single vessel disease. Patients with single vessel disease carry an improved prognosis and are therefore less likely to suffer recurrent ischemic events. It is interesting that the presence of stenosis, following thrombolysis for acute myocardial infarction, does not result necessarily in an increased incidence of inducible ischemia or symptoms during exercise testing. Sutton JM and Topol EJ in 1991 showed that only increased creatinine kinase levels predicted the absence of reversible ischemia during exercise testing. In addition, the presence of residual stenosis in single or multiple vessel disease was not predictive of inducible ischemia during exercise testing. A further study by Ellis SG et al. 1989, of patients recruited to the TIMI IIB study showed no increase in the incidence of recurrent ischemic events during hospital in-patient period in patients with TIMI -grade 2 or 3 or a significant residual stenosis who had not undergone PTCA or thrombolysis. A smaller study, however,(Grines CL et al. 1988) found significant residual stenosis in ≥ 50% was predictive of reocclusion. In this study, angiography was carried out at day-7 which may have influenced surprisingly high reocclusion rate of 23%. However, as there were only 50 patients in this study, the number of events recorded in each group was small, suggesting the possibility of a Type II error.

9.6 Number of Vessels Affected by Coronary Artery Disease:

The coronary angiogram at 24-hours with reference to the TIMI score of coronary artery stenosis of was used to define the number of affected vessels for each patient. If only the

infarct-related artery was affected, patients were defined as having single vessel disease regardless of the presence of a residual stenosis. It was not felt that the concept of no vessel disease was valid, given that an acute myocardial infarction had occurred in each patient, implying underlying atherosclerosis in the infarct-related artery at least. 19% of patients were shown to have triple vessel disease and 47% single vessel disease. Symptoms during exercise were unaffected by the number of diseased vessels. However, patients with three-vessel disease were more likely to have an ST-segment depression of ≥ 1 mm during exercise testing. Functional capacity was unrelated to the number of diseased vessels. Clinical outcome with three-vessel disease showed an increased incidence of all cardiac ischemic events as an out-patient, with 50% of patients experiencing at least one clinical event in this group. There was an increased mortality in patients with 3 vessel disease compared to with 1 and 2 vessel disease combined (22% v 6%) In the pre-thrombolytic era ST-segment depression at exercise testing post-myocardial infarction was shown to identify 90% of patients with triple vessel disease (Griffith LSC et al. 1997; Mannering D et al. 1987) Inadequate systolic blood pressure response was also associated with 3 vessel disease. In a study in younger patients [males ≤ 55yrs of age] only-32% of patients with multiple vessel disease could be identified by ST-segment depression during post-infarct exercise testing. This is possibly due to the low incidence of multi-vessel disease in this younger population. Prior to thrombolysis, myocardial necrosis and subsequent scar tissue formation following myocardial infarction, commonly resulting in area of non-viable myocardium. Therefore, reversible ischemia requiring viable myocardium implies additional vessel disease. Following thrombolysis, a residual stenosis subtending an area of viable myocardium is an additional reason for reversible ischemia during exercise testing. In TIMI II study following thrombolysis with or without PTCA patients with multi vessel disease were more likely to have ST segment depression during exercise testing (The TIMI Study Group, 1993) supporting the results of this present study. It still seems that despite thrombolysis patients with three-vessel disease and are more likely to have ST-segment depression during exercise testing However ST-segment depression during does not reliably detect the presence of three vessel disease with a low predictive accuracy of the positive test at 27%. The value of predischarge exercise testing is now in identifying patients with a

normal exercise response post infarct. The negative predictive accuracy remains high in the thrombolytic era at 89% identifying patients at low risk of recurrent cardiac events and a good prognosis who can be safely discharged from cardiological follow up.

9.7 Summary and Clinical Relevance

In the pre thrombolytic era the results of exercise testing post myocardial infarction were predictive of clinical outcome, risk stratification and extent of coronary artery disease. In this study 212 patients received thrombolysis within 6 hrs of the onset of symptoms of acute myocardial infection and underwent coronary angiography at 90 min and 24 hrs following therapy to determine patency of the infarct related artery and additional vessel disease. 156 of these patients were exercised before hospital discharge on a motorised treadmill using a symptom limited modified Bruce protocol. The results of the early invasive assessment and exercise testing were related and also used to predict clinical outcome. Patency of the infarct related artery: TIMI score 2,3, TIMI score 3 and early patency were not associated with exercise test variables but were predictive of a favourable clinical outcome in keeping with recent data from the Gusto study 1993. Residual stenosis of the infarct related artery failed to predict the exercise response or clinical outcome. Patients with 3 vessel disease had an increased incidence of ST segment depression during exercise testing. However the positive predictive value of ST segment depression was low in prediction of clinical outcome or identification of 3 vessel disease. The exercise test post myocardial infarction in the thrombolytic era retains its high negative predictive accuracy.

Thrombolysis results in reperfusion of an occluded infarct related artery at some point in time following therapy and salvage of myocardium at jeopardy of cell necrosis. Residual left ventricular function therefore depends on a number of factors: site of occlusion, time to reperfusion, degree of coronary patency, reocclusion and presence of a residual stenosis of infarct related artery. In the prethrombolytic era, left ventricular function was a major determinant of clinical outcome. Reversible ischemia on the exercise test was due to the presence of additional vessel disease. In the absence of reperfusion of infarct related artery a coronary occlusion will cause infarction of the myocardial muscle it supplies, healing with scar tissue formation. However, following thrombolysis a residual stenosis of the

infarct related artery offers an alternative reason for inducible ischemia if there is myocardial salvage and viable muscle.

The prognosis in patients with a residual stenosis subtending an area of viable myocardium, particularly with single vessel disease is likely to carry an improved prognosis compared to those patients with 3 vessel disease. It is therefore not surprising that reversible ischemia during the predischarge exercise testing now representing a variety of anatomical conditions, no longer has the same predictive accuracy. Thrombolysis improves mortality from myocardial infarction and in accordance with Bayes thoerum any test designed to identify an adverse outcome will result in a reduced positive predictive accuracy. A normal exercise test post myocardial infarction in the post thrombolytic era still identifies low risk patients with a good clinical outcome.

Therefore thrombolysis should be given for treatment of myocardial infarction with a view to achieving early and complete reperfusion to minimise left ventricular damage The exercise test should be performed post infarct, preferably prior to hospital discharge.

A normal exercise response identifies patients at low risk who can be discharged from cardiological follow up without further investigation. Patients with an very poor exercise capacity, significant early reversible ischemia or severe angina post infarct should be considered for further investigation to define coronary anatomy with a view to intervention. There remains an intermediate group of patients with moderate abnormalities on their exercise test who require a period of follow up under the cardiologist. This is needed to monitor the clinical progress of the patient before deciding to embark on further investigations or discharge the patient back to the general practitioner.

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1. APPENDIX I

1.1 COMPARISON OF ANISTREPLASE/STREPTOKINASE PROTOCOL

1. STUDY OBJECTIVES

1.1 To measure and compare angiographically documented coronary artery patency at 90 minutes following intravenous APSAC 30 Units or intravenous streptokinase 1.5 million units.

1.2 To compare reocclusion rates at 24 hours after dosing.

2. STUDY MEDICATION

2.1 **Intravenous APSAC**

APSAC is the active site p-anisoylated derivative of the primary (human) lys-plasminogen-streptokinase complex prepared by immediate acylation of the serine residue in the active centre of that complex as it is formed. The molecular weight is close to 131,000 Daltons.

APSAC is formulated in a mixture of clinical grade human albumin, D-mannitol and ly-lysine. It is presented in vials, each containing 30 Units APSAC as a sterile, white lyophilized powder.

2.2 **Storage**

APSAC 300 vials have a shelf-life of 2 years when stored at or below 5°C.

2.3 **Streptokinase**

Streptokinase is presented as a freeze-dried powder in vials containing 600,000 units of streptokinase. Streptokinase is stable for at least 3 years when stored at room temperature (<25°C). Solutions prepared for infusion but left over or not used should be discarded.

3. STUDY DESIGN

A double blind, double dummy, randomised, angiographically controlled study of intravenous APSAC or intravenous streptokinase in acute myocardial infarction with stratification according to infarct site.

3.1 Number of patients

A minimum of 809 patients will complete the study. One hundred and twenty-eight patients were recruited.

3.2 Patient Entry

Patients with clinical evidence of acute myocardial infarction who satisfy the inclusion/exclusion criteria will be eligible for randomisation.

3.3 Stratification and Randomisation

Patients will be stratified according to the site of infarction. Each stratum has been separately pre-randomised to receive APSAC 30 Units intravenous or streptokinase 1.5 million Units intravenous.

3.4 Coronary Angiography

Angiography will be performed at 90 minutes and at 24 hours after dosing.

3.5 Blood pressure and heart rate monitoring

Blood pressure and heart rate will be monitored immediately before drug and continuously throughout the 90 minutes post-treatment period. Blood pressure and heart rate will be recorded on the case report forms every 2 minutes until the end of the 90 minute angiogram.

3.6 Primary Data end Points

3.6.1. Angiographically documented patency (occlusion/perfusion grade 2,3) or occlusion (occlusion/perfusion grade 0.1) of the presumed infarct related vessel at 90 minutes after dosing.

3.6.2. Angiographically documented reocclusion (occlusion/perfusion grade 0,1) or sustained patency (occlusion/perfusion grade 2,3) at 24 hours after dosing in those who had patent infarct related vessels at 90 minutes.

4. PATIENTS AND METHODS

All patients with suspected acute myocardial infarction who satisfy the inclusion/exclusion criteria will be admitted.

5. INCLUSION CRITERIA

Patients admitted to hospital;

5.1 Aged 70 years or under.

5.2 With chest pain or other symptoms of acute myocardial infarction of at least 30 minutes duration who can be treated within 6 hours of symptom onset.

5.3 With ECG evidence of ST segment elevation of at least 0.1 mV in two or more standard leads and/or 0.2 mV in two or more praecordial leads.

5.4 In whom appropriate consent is obtained for participation in the study.

6. EXCLUSION CRITERIA

6.1 Patients with systolic blood pressure below 95 mmHg.

6.2 Patients on anticoagulant therapy.

6.3 Patients with a known history of haemorrhagic diatheses or significant recent bleeding from another site.

6.4 Patients with documented or suspected active peptic ulceration within 1 year.

6.5 Patients with a history of cerebrovascular accident.

6.6 Patients who have had surgery, major trauma or head injury within the previous months.

6.7 Patients who have received streptokinase or APSAC therapy within the previous 6 months.

6.8 Patients with severe hypertension, blood pressure above 200/120 mmHg.

6.9 Patients who have received prolonged chest compression prior to randomisation.

6.10 Pregnant females or those in whom pregnancy cannot be ruled out. Females who are menstruating or who are of child bearing potential.

6.11 Patients with diabetic proliferative retinopathy.

6.12 Patients in whom coronary angiography is contraindicated.

6.13 Patients who have had coronary angioplasty within 1 month of presentation or those with a history of CABG or prosthetic valve insertion.

6.14 Any condition requiring immediate surgical intervention.

6.15 any clinical suspicion of dissecting aneurysm.

6.16 transmural myocardial infarction within 3 months.

6.17 Patients with serious or life-threatening disease unrelated to the circulatory system.

7. CORONARY ANGIOGRAPHY

7.1 Coronary angiography will be via a brachial or femoral artery approach. At least three views (LCA) or two views (RCA) of the infarct related vessel will be taken during procedure. One of these will be the optimal view for maximising the percent residual stenosis.

7.2 An angiogram will be performed at 90 minutes from the start of dosing. The catheter will then be withdrawn, but the sheath will be left in place for up to 48 hours.

7.3 Patency will be defined by TIMI scoring at 90 mins and 24 hrs post thrombolysis. Grade 0, 1 is defined as non patent. Grade 2,3 as patent.

8. BLOOD PRESSURE MONITORING

Arterial pressure and heart rate will be recorded immediately before and continuously for 90 mins after dosing. Copies of all tracings will be reported in the relevant section of the case record from prior to their being placed in the inside cover.

9. HEPARIN ADMINISTRATION

All patients should receive heparin in a dose of 1000-1500 units per hour from between 4 and 6 hours after thrombolytic therapy or when the thrombin time has decreased to less than twice the control value.

Heparin treatment will be continued for 24 hours and further anticoagulation is at the physicians discretion.

10. ECG RECORDINGS

All patients will have single lead continuous ECG rhythm recordings for the first 24 hours of the study. Rhythm disturbances will be reported in the appropriate section of the case report form.

Five 12 lead ECG's are required, these include one on admission, at 2, 4, 16, 18 and 24 hours. If the patients clinical condition changes substantially within the first 24 hours, further ECG's may be required.

11. CLINICAL ASSESSMENTS

11.1 Any symptoms thought to be associated with the procedure, the treatment or the disease will be noted.

11.2 Heart rate and blood pressure will be measured before dosing and continually for the first 90 mins after dosing. There will be further non-invasive measurements at 6,12 and 24 hours after dosing or more frequently if indicated by a change in the patient's condition.

11.3 Temperature will be monitored at 6, 12 and 24 hours after dosing. Measurements will be taken more frequently if indicated by changes in the patient's condition.

12. LABORATORY OBSERVATIONS

Blood samples will be drawn to determine hepatitis B status, cardiac enzyme concentrations, clinical chemistry, haematology.

12,1 **Hepatitis B status**.

A blood sample will be taken before dosing and tested for HBsAg.

12.2 **Cardiac Enzymes Concentrations**

Blood samples must be taken before dosing, at 90 mins and 24 hours after dosing for the estimation of CPK and routine cardiac enzymes.

12.3 **Clinical Chemistry and Haematology**

Blood samples will be taken before dosing, at 90 mins and 24 hours after dosing for a routine screen.

12.4 **Urinalysis**

A urine sample will be collected at 24 hrs after dosing for the estimation of pH, blood, ketones, protein and bilirubin by means of "Dipstix".

13. PRECAUTIONS

13.1 **Ancillary medications**

No anti-platelet medication for 24 hrs after thrombolytic therapy.

Additional drugs, such as analgesics, antiarrhythmics etc., should be administered in accordance with normal hospital practice. All patients will receive a continuous infusion of intravenous nitrates.

13.2 **Dealing with excessive production of plasmin**

For the treatment of severe uncontrolled bleeding, it is suggested that the following steps be taken:

a) discontinue thrombolytic agent

b) application of local pressure where possible

c) reversal of the lytic state; Administer TRANEXAMIC ACID in a standard dose of 500 mg intravenously over 2 mins (other agents may be used). A further 500 mg tranexamic acid may be administered if the bleeding is not controlled after the replacement of clotting factors.

d) replace clotting factors with cryoprecipitate, fresh frozen plasma, or whole blood.

e) replace blood loss.

14. DRUG ACCOUNTABILITY

14.1 On-site Storage and Distribution

All investigational drug supplies will be stored in a refrigerator, maintained at 5°C at the study site. Shelf life for APSAC is 2 years. Access to the study medication must be limited to the principal investigator and other authorised members of his staff.

During periodic monitoring by Beecham staff, the drug supplies and case records will be reviewed for accuracy and completeness.

15. INFORMED CONSENT AND PATIENT PRIVACY

It is the investigator's responsibility that each subject or subject's legal representative signs an informed consent statement prior to participation in this study. Copies of the consent form with the patient's initials will be retained by the investigator.

The patients will be informed of their rights to privacy but will be made aware that study data will be submitted to Beecham and to drug regulatory authorities for review and evaluation. They will also be informed that both Beecham and

the regulatory authorities have the right to inspect the patient's medical records to verify the accuracy and completeness of the study records and results.

16. REPORTING OF ADVERSE EVENTS

The date, time of onset, duration and severity of any adverse reaction will be recorded. In the event of a persistent severe adverse event, e.g. hemiplegia resulting from CVA, the outcome should be determined at intervals up to 1 year.

1. APPENDIX 11

1.1 A PILOT STUDY OF BOLUS TPA 35mg x 2 IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION INTRODUCTION

OBJECTIVES

To assess the effect of two boluses of rt-PA on the patency of coronary vessels at 30, 60 and 90 minutes in patients with acute myocardial infarction by invasive and non invasive methods.

STUDY DESIGN

This study has an open dose-ranging design to evaluate bolus rt-PA. Initially 20 patients will be treated with two boluses, the initial bolus being 35 mg rt-PA. This would be repeated at 30 minutes, giving a total dose of 70 mg. Following the first 20 patient's treatment, the results will be analysed, and a further 20 patients will be treated at a further dosing level of 50 mg, repeated after 30 minutes. This dose increment will be dependent on the results obtained. The maximum total dose of rt-PA used in this study will be 100 mg, as is the recommended dose schedule at present used in clinical practice.

STUDY POPULATION

Inclusion Criteria

(1) Patients with acute myocardial infarction defined as:

a) Cardiac pain at rest lasting from thirty minutes up to six hours.

b) ECG changes at presentation consistent with a diagnosis of acute myocardial infarction.

Normally this will include ST segment elevation of at least 2 mm in two praecordial leads or ST segment elevation of 1 mm in two inferior leads.

However, patients with ECG diagnosis of posterior myocardial infarction and right ventricular myocardial infarction will also be included.

(ii) Males and females.

(iii) Age 18 to 75 inclusive.

(iv) Patients who have no contra-indications to angiography.

(v) Patients able to give informed consent to participate.

(vi) Patients with no history or ECG changes of previous myocardial infarction in same distribution.

(vii) Patients weighing over 67 kg.

Exclusion Criteria

(i) Patients with ECG abnormalities that make it impossible to diagnose acute myocardial infarction. This will include patients with left bundle branch block and other severe conduction defect abnormalities.

(ii) Patients with any contra-indications to thrombolytic therapy:

Any bleeding diathesis

Major trauma or surgery within three months

Puncture of a non-compressible vessel within 10 days

Any major haemorrhage

Any patient on Warfarin or Coumarin anticoagulants

Any previous cerebrovascular accident including TIA

Any previous history of peptic ulceration

Any proliferative retinopathy

Women who are pregnant, lactating or menstruating

History of severe poorly controlled hypertension

Any additional contraindication that is felt by the clinician to be relevant at that

time to bolus rt-PA therapy.

METHODS

The patients will be assessed pre-study within the Coronary Care Unit of Stobhill General Hospital. Thrombolytic therapy has been administered as standard therapy since 1982, and this study will be conducted within the Unit using standard monitoring facilities and general nursing medical care as appropriate. Written informed consent will be obtained from patients, both for administration of thrombolytic therapy, and also permission for performance of coronary arteriography. Where appropriate, and when available, the protocol and procedure will be discussed with any accompanying relatives.

The first bolus dose of rt-PA will be given as soon as possible following diagnosis. In addition, all patients will receive 150 mg of aspirin orally on admission. Analgesia will be given as per standard practice, and at no stage will any routine antiarrhythmic, inotropic nor vasodilator therapy be witheld. A second bolus dose of rt-PA will be given 30 minutes after the first bolus. At 3 hours following dosing, a bolus of heparin 5,000 units and an infusion of 1,000 units per hour will then be commenced with the rate of infusion being controlled using standard coagulation screens. The second bolus of therapy will not be administered if there are any new contra-indications such as the occurrence of bleeding, cerebrovascular accident or if any surgical intervention is required.

Coronary arteriography will be performed 30 minutes after the infusion of rt-PA. An angiogram of the culprit vessel, as judged by the admission ECG, will be performed, and a second bolus dose will be administered thereafter. An arterial sheath will be left in situ, and the coronary arteriogram continued with further angiograms performed at 45, 60 and 90 minutes. The arterial sheath will be left in situ, and coronary angiography will be repeated at 24 hours.

At all times the performance of coronary angiography will be undertaken if the patient's clinical condition is stable, and the investigation appropriate. Any form of medical or intervention therapy can be performed at any time at the discretion of the Consultant Cardiologist managing the patient's overall condition.

Standard twelve lead ECGs will be performed at 0 time, time 2 hours, 4 hours, 8 hours, 12 hours and 24 hours following dosing. Serial cardiac enzymes will be performed, including CPK, AST, ALT and LDH at 4, 12 and 24 hours following admission to confirm diagnosis of acute myocardial infarction. Routine haematology and biochemistry will be performed as required for patient management, and a coagulation status will be performed to allow anticoagulation.

Standard electrocardiographic monitoring with Holter monitor will be performed for 24 hours, and this data will be analysed by Reynolds Pathfinder to correlate ST segment changes with the reperfusion data obtained from coronary angiography.

All clinical events will be monitored and the patient's follow up therapy will be undertaken as deemed appropriate by the Cardiologist.

The coronary arteriograms will be analysed blindly to assess the achievement of reperfusion, and to assess the relative degree. In addition, the morphological appearance of the coronary artery following reperfusion will also be assessed using standard techniques, as previously performed in the European Collaborative Study for Tissue Plasminogen Activator.

1. APPENDIX III

1.1 PATIENT INFORMATION SHEET: THROMBOLYTIC THERAPY

A heart attack or a coronary thrombosis is the term used for a condition in which the flow of blood to the heart muscle is reduced to a degree that damage occurs. The reduction in blood flow is usually due to a blood clot or thrombus obstructing the arteries leading to the heart muscle. After a period of time, damage is irreversible and the course of the illness will follow the normal healing process. If a patient is admitted to hospital early enough, then treatment may be introduced which can dissolve the blood clot and can restore flow of blood to the area of muscle under threat of permanent damage.

The standard treatment for heart attack within the Coronary Care Unit of Stobhill Hospital is to give this therapy to dissolve the blood clot - that is thrombolytic treatment, to those patients admitted in the early stage of coronary thrombosis to obtain coronary artery flow, and to reduce the degree of damage. This form of treatment cannot be given to patients who have a predisposition to bleeding, such as those with stomach or duodenal ulcers, or to patients who have had strokes or operations in the recent past.

Two standard drugs are available at present for thrombolytic therapy called Streptokinase and Tissue Plasminogen Activator. This latter drug has been shown to be very successful in dissolving blood clots, and has been used in a widespread manner in both United States and mainland Europe, as well as in the U.K. We use thrombolytic treatment only in those cases who should benefit, and who have no contra- indication. This treatment is in addition to all normal forms of treatment. Although we are studying Tissue Plasminogen Activator, its use will not prevent the introduction of any other treatment which is necessary for the underlying condition. To maximise the dose of Tissue Plasminogen Activator to be given to any patient, we are studying its effects on blood clotting, and therefore frequent blood sampling is taken from a small plastic tube inserted in the arm.

As a follow up to thrombolytic therapy to assess its success and to determine if any other procedures or treatment should be given, an x-ray test, called a coronary arteriogram, is often helpful and we are performing this as part of the present study. This requires the insertion of a little plastic tube into an artery, and therefore signed consent is required before the performance of this test. The actual method of the test will be explained separately by the Doctor who will perform the procedure at the time.

CONSENT FORM

I .....of .....

hereby consent to receive the thrombolytic agent to undergo the procedure of coronary arteriography, the nature and effect of which have been explained to me by Dr. ..... I consent to the administration of a local anaesthetic for these purposes. I also consent to such further or alternative procedures which may be found to be necessary during the course of the arteriogram.

Date ..... Signed .....

I confirm that I have explained to the patient the proposed nature and effect of this therapy and the procedure of coronary arteriography.

Date ..... (Doctor's Signature) .....

1. APPENDIX IV

1.1 DEFINITION OF TIMI SCORES

(Williams et al., 1986)

GRADE 0 **NO REPERFUSION**: There is no antegrade flow beyond the point of occlusion.

GRADE 1 **PENETRATION WITH MINIMAL PERFUSION**: The contrast material passes beyond the area of obstruction, but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for duration of the cine run.

GRADE 2 **PARTIAL PERFUSION:** The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry or clearance from comparable areas not perfused by the previously occluded vessel, e.g. the opposite coronary artery or the coronary bed proximal to the obstruction.

GRADE 3 **COMPLETE PERFUSION**: Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed is as rapid as clearance from an uninvolved bed as the same vessel or the opposite artery.

APPENDIX V

Timi Scoring for Coronary Artery Stenosis

Score	Coronary Artery Stenosis
0	Normal
1	<50%
2	50-90%
3	91-99% (complete filling)
4	91-99% (incomplete filling)
5	100%
6	absent
7	unknown

APPENDIX VI

EXERCISE TEST PROTOCOLS

BRUCE PROTOCOL

STAGE	SPEED (mph)	GRADE (%)	DURATION (minutes)
1	1.7	10	3
2	2.5	12	3
3	3.4	14	3
4	4.2	16	3
5	5.0	18	3
6	5.5	20	3
7	6.0	22	3

MODIFIED BRUCE PROTOCOL

STAGE	SPEED (mph)	GRADE (%)	DURATION (minutes)
1	1.7	0	3
2	1.7	5	3
3	1.7	10	3
4	2.5	12	3
5	3.4	14	3
6	4.2	16	3
7	5.0	18	3
8	5.5	20	3
9	6.6	22	3

APPENDIX VII

RAW DATA

Demographic Data

Patency Scores

Exercise Variables

Residual Stenosis and Vessel Disease

Cardiac Event Dates

Demographic Data

Median age

1 indicates ≥ median age

0 indicates < median age

Sex

1 male

2 female

Reciprocal depression

1 present

0 absent

Time to therapy

1 indicates <2hrs or <4hrs

2 indicates ≥2hrs or >4hrs

Infarct related artery

1 LAD

2 RCA

3 CX

Infarct site

1 anterior

2 inferior

Patient No	Age >Median	Sex	Reciprocal Depression	Time to Therapy <2hrs	Time to Therapy <4hrs	Infarct Related artery	Infarct Site
1	1	1	1	2	1	2	1
2	1	1	1	2	2	2	1
3	0	1	1	2	1	2	1
4	0	1	0	2	2	1	2
5	1	2	1	2	1	2	1
6	0	1	1	1	1	2	1
7	0	1	1	2	2	2	1
8	0	1	1	1	1		2
9	1	1	0	2	1	1	2
10	1	1	0	2	1	2	1
11	1	1	1	2	1	2	1
12	0	1	1	2	1	2	1
13	1	1	1	1	1	1	
14	1	2	1	2	1	1	1
15	1	1	1	2	2	1	2
16	0	1	1	2	2	2	1
17	1	1	1	2	1	2	1
18	0	1	0	2	1	1	2
19	0	2	0	2	2		2
20	0	1	0	2	1	1	2
21	0	1	0	2	2	1	2
22	0	1	1	2	1	2	1
23	0	1	1	2	2	2	1
24	0	1	1	1	1	2	1
25	0	1	1	2	2	3	1
26	0	1	1	2	1	2	1
27	0	1	0	2	2	2	1
28	0	1	1	2	2	2	1
29	1	1	1	2	2	1	2
30	0	2	1	2	1	1	2
31	1	2	1	2	1	2	1
32	1	2	1	2	1	2	1
33	1	1	1	2	2	1	2
34	0	1	0	2	1	1	2
35	0	1	1	2	1	1	
36	1	1	1	2	1	2	1
37	1	1	1	2	2	2	1
38	0	1	1	2	1	1	2
39	0	1	1	2	1	2	1
40	1	2	0	2	1	2	1
41	1	1	1	2	2	1	2
42	0	1	0	2	2	2	1
43	0	2	0	2	2	2	1

Patient No	Age >Median	Sex	Reciprocal Depression	Time to Therapy <2hrs	Time to Therapy <4hrs	Infarct Related artery	Infarct Site
44	1	2	1	1	1	2	1
45	0	1	0	2	1	1	2
46	1	1	1	2	2	1	2
47	0	1	1	2	1	1	2
48	1	1	1	1	1	2	1
49	1	2	1	2	2	3	1
50	1	1	0	2	1	2	1
51	1	1	1	2	1	2	1
52	0	1	1	2	1	2	1
53	1	1	1	2	2	1	
54	1	2	1	2	1	2	1
55	0	1	0	2	1	1	1
56	0	1	0	2	1		2
57	1	1	0	1	1	1	2
58	0	1	0	2	2	1	2
59	0	1	1	2	1	2	1
60	1	2	1	2	2	3	1
61	1	2	0	2	2	1	2
62	0	1	1	2	1	2	1
63	1	2	1	2	1	3	1
64	1	1	1	2	2	2	1
65	1	1	0	2	2	1	2
66	1	1	0	2	1	1	2
67	0	1	1	2	1	1	2
68	0	1	0	2	1	1	2
69	0	1	0	2	2	3	2
70	1	1	0	2	2		1
71	1	1	0	2	1	1	2
72	1	1	1	1	1	2	1
73	0	1	1	1	1	1	2
74	1	1	1	2	2	1	2
75	1	2	0	2	1	1	2
76	1	1	0	2	2	1	2
77	1	2	1	2	1	2	1
78	0	1	0	2	1	1	2
79	0	1	0	2	2	2	1
80	0	1	1	2	2	2	
81	1	1	0	2	1	3	1
82	0	1	1	2	1	2	1
83	1	1	1	2	2	1	2
84	1	1	1	2	1	3	1
85	1	2	1	1	1	2	1
86	0	1	1	1	1	2	1

Patient No	Age >Median	Sex	Reciprocal Depression	Time to Therapy <2hrs	Time to Therapy <4hrs	Infarct Related artery	Infarct Site
87	1	1	0	2	2	1	2
88	1	1	0	2	2	1	2
89	0	1	1	2	1	1	2
90	1	1	0	2	1	1	2
91	0	1	1	2	1	3	1
92	1	1	0	2	1		2
93	1	1	1	2	1	2	1
94	0	1	1	1	1	2	1
95	0	1	1	2	1	1	2
96	1	2	0	2	1	1	2
97	1	2	0	2	1	1	2
98	0	1	0	2	1	1	2
99	0	1	1	2	1	1	2
100	0	1	0	1	1	1	2
101	1	2	1	2	1	1	2
102	1	1	0	2	2	1	2
103	0	1	1	2	1	2	
104	1	1	0	1	1	3	1
105	1	1	1	2	1	2	1
106	0	2	1	2	1	2	1
107	0	1	1	2	1	1	2
108	0	1	0	2	1	2	1
109	0	2	1	2	2	2	1
110	0	2	1	2	1	2	1
111	0	2	1	2	1	1	2
112	0	1	0	2	1	2	1
113	0	1	1	2	1	2	1
114	1	1	1	1	1	2	1
115	1	2	1	2	2		
116	1	1	0	2	1		2
117	0	1	1	2	1	3	1
118	1	1	1	2	1	3	1
119	0	1	0	2	1	1	2
120	0	1	0	2	2	1	2
121	1	1	1	2	2	2	1
122	0	2	1	2	1	2	1
123	1	1	0	2	2	1	2
124	1	2	1	2	1	2	1
125	1	1	0	2	1	1	2
126	1	1	1	1	1	1	
127	1	1	0	2	1	1	2
128	1	1	1	2	1	1	2
129	0	1	0	2	2	1	2

Patient No	Age >Median	Sex	Reciprocal Depression	Time to Therapy <2hrs	Time to Therapy <4hrs	Infarct Related artery	Infarct Site
130	1	2	0	2	2	1	2
131	1	2	0	2	1	3	2
132	1	2	1	2	2	2	1
133	0	1	0	2	1	3	2
134	0	2	0	2	2	1	2
135	1	2	0	2	1	1	2
136	0	1	0	2	1	1	2
137	1	1	1	2	1	2	1
138	1	1	0	1	1		1
139	1	1	1	1	1	2	2
140	1	1	1	2	1	1	2
141	0	1	0	1	1	2	1
142	1	1	1	2	2	2	
143	1	1	0	2	2	2	1
144	1	1	0	2	2	1	2
145	1	1	1	2	1	1	2
146	0	1	1	2	1	1	2
147	0	1	0	2	1	1	2
148	0	1	1	2	1	2	
149	0	1	0	1	1	1	2
150	1	1	1	2	1	2	1
151	0	1	1	2	1	2	1
152	1	1	0	2	2	1	2
153	0	1	1	2	1	2	1
154	1	1	0	2	2	2	1
155	1	2	0	2	2		1
156	0	1	0	2	1	2	1
157	1	1	1	2	1	3	
158	0	1	1	2	2		
159	0	2	1	2	2	2	1
160	1	2	1	2	1	2	1
161	0	2	1	2	1	2	1
162	1	1	0	2	1	2	1
163	1	2	0	2	1	1	2
164	1	2	1	2	2	2	1
165	1	2	1	1	1	2	
166	1	1	1	2	1	2	1
167	1	2	0	2	1	1	2
168	0	1	1	1	1	1	2
169	0	1	0	1	1	1	2
170	0	2	1	2	1	2	1
171	1	2	0	2	2	2	1
172	0	1	1	2	1		2

Patient No	Age >Median	Sex	Reciprocal Depression	Time to Therapy <2hrs	Time to Therapy <4hrs	Infarct Related artery	Infarct Site
173	0	1	1	1	1	1	2
174	1	1	1	1	1	2	1
175	1	1	0	2	2	1	2
176	0	1	0	1	1	1	2
177	0	2	1	2	2	2	1
178	0	1	0	2	1	1	2
179	1	1	1	2	1	2	1
180	1	1	1	2	1	3	1
181	1	2	0	2	2	2	1
182	1	2	0	2	1	2	1
183		1	1	2	1	2	1
184	1	2	1	2	2	2	
185	0	1	1	1	1	1	
186	1	2	1	2	2	2	1
187		1	1	2	1	1	2
188	1	2	1	2	2	2	1
189	0	1	0	2	1	1	2
190	0	1	1	2	1	1	2
191	0	1	1	2	1	1	2
192	0	1	0	2	1	1	2
193		1	1	2	1	2	1
194	0	1	1	2	1	2	1
195	0	1	0	2	2	1	2
196	0	1	1	2	1	1	
197	0	1	1	2	1	1	2
198	0	1	1	2	2	1	
199	1	1	1	2	1	2	1
200	0	1	1	2	2	2	1
201	1	1	1	2	1	1	
202		1	1	2	2	1	
203	0	1	0	2	2	2	1
204	1	1	1	2	1	1	2
205	0	1	1	2	2	1	2
206	1	1	1	2	2	2	1
207	0	1	1	2	1	2	1
208		2	1	2	1	1	2
209	1	2	1	2	1		
210	1	2	1	2	1	2	1
211		1	1	2	2	2	1
212		1	1	2	1	1	2

Patencey Data

TIMI Score

As defined by appendix IV

Patency Status

1 indicates a patent artery (timi score 2 or 3)

0 indicates a non patent artery (timi score 0 or 1)

TIMI Score 3

3 indicates TIMI Score 3

0 indicates timi score O,1,2

Patient NO	TIMI Score 90 min	TIMI Score 24 hrs	Patency Status	Patency 90 min	Patency 24 hrs	TIMI Score 3 90 min
1	0	1	0	0	0	0
2	3	3	1	1	1	3
3	3			1		3
4	3	3	1	1	1	3
5	0	3	2	0	1	0
6	3	3	1	1	1	3
7	0	3	2	0	1	0
8						
9	0	0	0	0	0	0
10	2	0	3	1	0	0
11	0	3	2	0	1	0
12	3	3	1	1	1	3
13	0			0		0
14	0	0	0	0	0	0
15	2	3	1	1	1	0
16	3	3	1	1	1	3
17	0	3	2	0	1	0
18	3	3	1	1	1	3
19						
20	0	2	2	0	1	0
21	2	3	1	1	1	0
22	0	3	2	0	1	0
23	3	3	1	1	1	3
24	3	3	1	1	1	3
25	3	3	1	1	1	3
26	3	3	1	1	1	3
27	0	0	0	0	0	0
28	2	3	1	1	1	0
29	0	2	2	0	1	0
30	3	3	1	1	1	3
31	0			0		0
32	3	3	1	1	1	3
33	3	3	1	1	1	3
34	3	3	1	1	1	3
35	0	1	0	0	0	0
36	0			0		0
37	3	3	1	1	1	3
38	0			0		0
39	0	3	2	0	1	0
40	0			0		0
41	0	2	2	0	1	0
42	3	3	1	1	1	3
43	0	0	0	0	0	0

Patient NO	TIMI Score 90 min	TIMI Score 24 hrs	Patency Status	Patency 90 min	Patency 24 hrs	TIMI Score 3 90 min
44	3	3	1	1	1	3
45	2	3	1	1	1	0
46	2	2	1	1	1	0
47	0	3	2	0	1	0
48	3	3	1	1	1	3
49		3			1	
50		2			1	
51	0	1	0	0	0	0
52	3	3	1	1	1	3
53	0			0		0
54	0	3	2	0	1	0
55	1	3	2	0	1	0
56						
57	1	3	2	0	1	0
58	3	3	1	1	1	3
59	1	3	2	0	1	0
60	0	3	2	0	1	0
61	1	2	2	0	1	0
62		0			0	
63	3	3	1	1	1	3
64	0	2	2	0	1	0
65	3	3	1	1	1	3
66	3	2	1	1	1	3
67	1	2	2	0	1	0
68	1	3	2	0	1	0
69	3	3	1	1	1	3
70						
71	0	2	2	0	1	0
72	3	3	1	1	1	3
73	3	3	1	1	1	3
74	3	3	1	1	1	3
75	3	3	1	1	1	3
76	3	3	1	1	1	3
77	3	3	1	1	1	3
78	3	3	1	1	1	3
79	0	3	2	0	1	0
80	2	3	1	1	1	0
81	0	3	2	0	1	0
82	3	3	1	1	1	3
83	0	2	2	0	1	0
84	0	3	2	0	1	0
85	0	3	2	0	1	0
86	3	0	3	1	0	3

Patient NO	TIMI Score 90 min	TIMI Score 24 hrs	Patency Status	Patency 90 min	Patency 24 hrs	TIMI Score 3 90 min
87	0	2	2	0	1	0
88	0	0	0	0	0	0
89	2	2	1	1	1	0
90	2	3	1	1	1	0
91	3	3	1	1	1	3
92						
93	3	3	1	1	1	3
94	0	0	0	0	0	0
95	2	2	1	1	1	0
96	1	2	2	0	1	0
97	2	3	1	1	1	0
98	0	1	0	0	0	0
99		3			1	
100	3	3	1	1	1	3
101	3	3	1	1	1	3
102	0	3	2	0	1	0
103	3	3	1	1	1	3
104	3	3	1	1	1	3
105	1	0	0	0	0	0
106		0			0	
107	2	2	1	1	1	0
108	2	2	1	1	1	0
109	0	3	2	0	1	0
110	3	3	1	1	1	3
111	0	3	2	0	1	0
112	2	3	1	1	1	0
113	3	3	1	1	1	3
114	3	3	1	1	1	3
115						
116						
117	0	0	0	0	0	0
118	0	0	0	0	0	0
119	1	3	2	0	1	0
120	0	0	0	0	0	0
121	2	3	1	1	1	0
122	0	3	2	0	1	0
123	2	3	1	1	1	0
124	2	2	1	1	1	0
125	3	3	1	1	1	3
126	3	3	1	1	1	3
127	1	2	2	0	1	0
128	3	3	1	1	1	3
129	3	3	1	1	1	3

Patient NO	TIMI Score 90 min	TIMI Score 24 hrs	Patency Status	Patency 90 min	Patency 24 hrs	TIMI Score 3 90 min
130	3	3	1	1	1	3
131	0	0	0	0	0	0
132	2	2	1	1	1	0
133	3			1		3
134	2	3	1	1	1	0
135	3	3	1	1	1	3
136	2	3	1	1	1	0
137	2	2	1	1	1	0
138						
139		2			1	
140	3	2	1	1	1	3
141	0	0	0	0	0	0
142	2	2	1	1	1	0
143	3	3	1	1	1	3
144	2	2	1	1	1	0
145	2	2	1	1	1	0
146	2	2	1	1	1	0
147	3	3	1	1	1	3
148	2	2	1	1	1	0
149	2	2	1	1	1	0
150	2	3	1	1	1	0
151	2	3	1	1	1	0
152	2	1	3	1	0	0
153	2	1	3	1	0	0
154	3	3	1	1	1	3
155						
156	2	1	3	1	0	0
157	0	2	2	0	1	0
158						
159	3	3	1	1	1	3
160	1	2	2	0	1	0
161	3	3	1	1	1	3
162	2	2	1	1	1	0
163	2	2	1	1	1	0
164	0	0	0	0	0	0
165	0	0	0	0	0	0
166	2	2	1	1	1	0
167	0	2	2	0	1	0
168	0	3	2	0	1	0
169	0	3	2	0	1	0
170	2	2	1	1	1	0
171	2	3	2	1	1	0
172						
173	3	3	1	1	1	3

Patient NO	TIMI Score 90 min	TIMI Score 24 hrs	Patency Status	Patency 90 min	Patency 24 hrs	TIMI Score 3 90 min
174	2	3	1	1	1	0
175	3	3	1	1	1	3
176	1			0		0
177	1	0	0	0	0	0
178	1	2	2	0	1	0
179	2	0	3	1	0	0
180	0	3	2	0	1	0
181	3			1		3
182	2	3	1	1	1	0
183	2	3	1	1	1	0
184	2	3	1	1	1	0
185	3			1		3
186	2	3	1	1	1	0
187	0	1	0	0	0	0
188	3	2	1	1	1	3
189	3			1		3
190	0	2	2	0	1	0
191	0	0	0	0	0	0
192	0	0	0	0	0	0
193	2	3	1	1	1	0
194	3	2	1	1	1	3
195	2	2	1	1	1	0
196	2	2	1	1	1	0
197	0	0	0	0	0	0
198	0	3	2	0	1	0
199	2	2	1	1	1	0
200	3	3	1	1	1	3
201	2	3	1	1	1	0
202	3	3	1	1	1	3
203	2	2	1	1	1	0
204	2	2	1	1	1	0
205	2	2	1	1	1	0
206	3	3	1	1	1	3
207	3	3	1	1	1	3
208	0	2	2	0	1	0
209						
210	0			0		0
211	3	3	1	1	1	3
212	3	3	1	1	1	3

No of diseased arteries and residual stenosis

No of diseased arteries

1 single vessel disease

2 double vessel disease

3 triple vessel disease

blank represents missing data

residual stenosis in single vessel disease

0 no stenosis or stenosis < 50% of luminal diameter

11 residual stenosis ≥ 50%

4 occluded vessel

residual stenosis with additional vessel disease

0 no stenosis or stenosis < 50% of luminal diameter

1 residual stenosis ≥ 50%

2 occluded vessel

Patient NO	NO of Diseased Arteries	Residual Stenosis of IRA in Single Vessel disease	Residual Stenosis of IRA +/- additional Vessel disease
1	1	11	1
2	2		1
3			
4	2		1
5	1	0	0
6	1	11	1
7	1	11	1
8			
9	2		2
10	1	4	2
11	2		0
12	1	0	0
13			
14	3		2
15	2		1
16	1		1
17	1	11	1
18	1	0	0
19			
20	2		1
21	1	11	1
22	3		1
23	2		0
24	2		1
25	1	11	1
26	1	11	1
27	1	4	2
28	1	11	1
29	1	11	1
30	1	0	0
31			
32	1	11	1
33	1	0	0
34			
35	2		1
36			
37	3		1
38			
39	1	0	0
40			
41			
42	3		1

Patient NO	NO of Diseased Arteries	Residual Stenosis of IRA in Single Vessel disease	Residual Stenosis of IRA +/- additional Vessel disease
43	1	4	2
44	2		1
45	1	0	0
46	2		1
47	1	11	1
48	1	11	1
49	2		1
50	2		1
51	1	11	1
52	2		0
53			
54	1	11	1
55	1	11	1
56			
57	1	11	1
58	1	0	0
59	3		1
60	3		1
61	2		1
62	2		2
63	3		1
64	2		1
65	1	11	1
66	3		1
67	1	0	0
68	2		1
69	1	0	0
70			
71	2		1
72	1	11	1
73	1	11	1
74	2		1
75	1	11	1
76	2		1
77	2		1
78	2		1
79	1	11	1
80	1	0	0
81	1	11	1
82	3		0
83	3		1
84	3		0

Patient NO	NO of Diseased Arteries	Residual Stenosis of IRA in Single Vessel disease	Residual Stenosis of IRA +/- additional Vessel disease
85	3		1
86	1	4	2
87	2		1
88	3		2
89	1	11	1
90	1	11	1
91	1	11	1
92			
93	3		1
94	3		2
95	1	11	1
96	1	11	1
97	1	11	1
98	1	4	2
99	1	11	1
100	1	11	1
101	2		1
102	2		1
103	1	11	1
104	1	11	1
105	1	4	2
106	2		2
107			
108	2		1
109	1	11	1
110	1	0	0
111	1	11	1
112	1	0	0
113	1	11	1
114	1	11	1
115			
116			
117	1	4	2
118	2		2
119	1	11	1
120	1	4	2
121	2		1
122	3		1
123	1	11	1
124	1	11	1
125	1	11	1
126	1	11	1

Patient NO	NO of Diseased Arteries	Residual Stenosis of IRA in Single Vessel disease	Residual Stenosis of IRA +/- additional Vessel disease
127	1	11	1
128	1	0	0
129	2		2
130	1	11	1
131	1	0	0
132	1	11	1
133			
134	1	11	1
135	1	11	1
136	3		0
137	1	11	1
138			
139	3		1
140	1	11	1
141	1	4	2
142	1	11	1
143	1	0	0
144	1	11	1
145	2		1
146	1	11	1
147	1	11	1
148	1	11	1
149	2		0
150	3		1
151	1	0	0
152	2		1
153	1	11	1
154	3		1
155			
156	3		1
157	2		1
158			
159	2		1
160	1	11	1
161	1	0	0
162	1	11	1
163	1	11	1
164	3		2
165	3		2
166	1	11	1
167	2		1
168	2		1

Patient NO	NO of Diseased Arteries	Residual Stenosis of IRA in Single Vessel disease	Residual Stenosis of IRA +/- additional Vessel disease
169	1	11	1
170	1	11	1
171	3		1
172			
173	3		0
174	1	11	1
175	1	0	0
176			
177	2		2
178	1	11	1
179	1	4	2
180	2		1
181			
182	2		1
183	2		1
184	2		1
185	2		1
186	3		1
187	1	11	1
188	2		1
189	2		1
190	2		1
191	2		2
192	2		2
193	1	11	1
194	1	11	1
195	3		1
196	3		1
197	2		2
198	2		1
199	3		1
200	2		1
201	1	11	1
202	1	11	1
203	1	11	1
204	2		0
205	1	11	1
206	1	11	1
207	2		1
208	2		1
209			
210			
211	3		1
212	2		1

Exercise Variables

CODES for all exercise variables

1 indicates the variables is present

0 indicates the variable is absent

Blank indicates missing data

Patient No	Exercise TIme > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
1								0		
2	0		0	0	0			1	0	0
3								0		
4	0		0	1	0			1	1	0
5	0		0	0	0			1	1	0
6	0		1	0	1			1	1	0
7	0		0	1	0			1	1	0
8								0		
9	1		0	0	1			1	1	0
10								0		
11	0	1	1	0	1			1	1	1
12	1	1	0	0	0			1	0	0
13								0		
14								0		
15	0	0	0	0	0			1	0	0
16	0	0	0	0	0			1	1	0
17								0		
18	1		0	0	1			1	1	0
19								0		
20	0		0	0	0			1	0	0
21	0		0	1	0			1	1	0
22	0		1	0	0	1	0	1	1	0
23	0		0	0	0			1	0	0
24	0		1	0	0	1	0	1	1	0
25	0		0	1	0	1	1	1	0	0
26								0		
27								0		

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
28								0		
29								0		
30	0		0	0	0	0	0	1	1	0
31								0		
32								0		
33	0	0	0	1	1			1	0	0
34								0		
35	0	0	0	0	1			1	0	0
36	1	1	1	1	1	1	1	1	1	0
37	1	0	1	1	0			1	1	0
38	1	0	0	1	0			1	1	0
39	1	1	1	1	1			1	0	0
40								0		
41								0		
42	1	1	0	1	0	0	0	1	0	0
43								0		
44								0		
45								0		
46								0		
47								0		
48	0	0	0	0	0	0	0	1	1	1
49								0		
50	1	1	1	0	1	0	1	1	1	0
51	1	1	0	0	1	1	1	1	0	0
52	1	1	0	0	1	1	1	1	0	0
53								0		

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
54	1	1	0	0	0	0	0	1	1	0
55	1	1	0	0	1			1	0	0
56	0	0	0	1	0			1	1	0
57	1	1	0	1	1			1	0	0
58	0	0	0	0	0			1	1	0
59	1	1	0	0	0			1	1	1
60								0		
61								0		
62	1	1	1	0	0			1	1	0
63								0		
64	1	1	1	0	0			1	0	0
65	0	0	0	0	0	1	1	1	0	0
66	1	1	1	0	0			1	0	0
67	0	1	0	0	0			1	1	0
68	1	1	0	1	1			1	0	0
69	1	1	0	0	1	1	1	1	0	0
70								0		
71	1	0	0	1	0			1	1	1
72	0	0	1	0	1			1	1	0
73	0	0	0	1	1			1	0	0
74								0		
75	0	0	1	1	1	1	1	1	1	0
76	1	1	0	0	0			1	1	0
77	1	1	0	0	0	0	1	1	0	0
78	0	0	0	0	0			1	1	0
79	1	1	0	0	0			1	1	1

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
80	1	1	1	0	0			1	0	0
81	0	0	1	0	0			1	1	0
82	0	0	1	0	1			1	1	0
83	0	0	1	1	1	0	0	1	1	0
84								0		
85								0		
86	0	0	1	0	0			1	1	1
87	0	0	0	1	0			1	0	0
88	0	0	0	0	0	1	0	1	1	0
89	1	0	1	1	1	1	0	1	0	0
90	0	0	0	1	1	0	0	1	0	0
91	0	0	1	0	0			1	1	1
92								0		
93	0	0	1	1	1			1	1	0
94	0	0	1	0	0			1	0	0
95	1	1	0	1	1			1	0	0
96	0	0	0	0	1			1	1	0
97	1	0	0	1	0	1	0	1	1	0
98	1	0	0	1	1	1	0	1	0	0
99	1	1	0	0	0			1	1	0
100	1	1	0	1	1	0	0	1	0	0
101	0	0	1	0	1	0	0	1	1	1
102	1	1	1	0	1			1	1	0
103	1	1	0	0	0			1	1	1
104	1	1	0	0	0	0	1	1	1	0
105								0		

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
106	0	1	1	0	0			1	1	0
107								0		
108	1	1	0	0	0			1	0	0
109	1	1	1	0	0			1	1	0
110	1	1	0	0	0	1	1	1	0	0
111	1	1	1	0	0			1	1	0
112	1	1	1	0	1			1	0	0
113	1	1	1	0	0			1	0	0
114	1	1	1	0	1	1	0	1	1	1
115								0		
116								0		
117	1	1	1	0	0			1	1	1
118	1	1	1	0	0			1	0	0
119	1	0	0	1	1	0	0	1	1	0
120	1	1	0	1	1			1	1	0
121	0	0	1	0	1	1	1	1	1	0
122	1	1	1	0	0			1	0	0
123	0	0	0	1	1			1	1	1
124	1	1	0	0	1			1	1	0
125								0		
126	1	0	1	0	0			1	0	0
127	0	0	0	1	1			1	0	0
128	1	1	0	1	1			1	0	0
129	1	1	0	0	0			1	0	0
130								0		
131	1	1	0	0	0			1	1	0

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
132	1	1	0	0	0			1	0	0
133	0	0	1	0	1			1	1	1
134	0	0	0	0	1	0	0	1	1	0
135	1	1	0	0	1			1	1	0
136	0	0	1	1	1			1	0	0
137								0		
138	1	1	0	0	0	1	1	1	0	0
139								0		
140								0		
141	1	1	0	0	0			1	0	0
142								0		
143	0	0	1	0	0			1	1	0
144	0	0	0	0	1			1	1	0
145								0		
146	1	0	0	1	1			1	0	0
147	1	1	0	0	1			1	1	0
148	0	0	0	0	0			1	0	0
149	1	0	0	0	0			1	1	1
150	0	0	1	0	0	0	0	1	1	1
151	1	0	0	0	0			1	1	0
152	0	0	0	0	0			1	0	0
153								0		
154	0	0	1	0	0	1	1	1	1	1
155	1	0	0	1	0			1	1	0
156	1	1	0	0	0	0	0	1	0	0
157	0	0	1	0	0	0	0	1	0	0

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
158								0		
159	1	1	1	0	1			1	0	0
160	0	0	0	0	0			1	0	0
161	0	0	1	0	1	0	0	1	0	0
162	1	1	0	0	1	1	0	1	1	0
163	0	0	0	0	1			1	1	0
164								0		
165	1	1	1	0	1	0	0	1	0	0
166	1	0	1	0	0	1	1	1	1	0
167	1	0	0	1	1			1	0	0
168	0	0	1	0	0	0	0	1	1	1
169								0		
170	1	1	0	0	1			1	1	0
171								0		
172	1	1	0	0	0	1	1	1	1	0
173	1	1	0	0	1			1	1	1
174	1	1	1	0	1			1	0	0
175	1	1	0	1	1			1	0	0
176								0		
177								0		
178	1	1	1	1	0			1	0	0
179								0		
180	1	1	1	0	0			1	0	0
181	0	0	0	0	0			1	1	0
182	1	0	0	0	0			1	0	0
183	0	0	1	0	0			1	1	0

Patient No	Exercise Time > Median	Mets >Median	ST Depression	ST Elevation	T wave Normalisation	Rate Pressure Product > 8500	Systolic BP Rise >30mmhg	No ETT	Symptoms Combined	Angina
184								0		
185	0	0	0	1	1			1	1	0
186	0	0	0	0	1			1	1	0
187	1	1	0	0	1			1	0	0
188	1	0	0	0	0	0	0	1	0	0
189	0	0	1	1	0			1	0	0
190	1	1	0	0	1			1	0	0
191	0	0	1	1	0	0	0	1	0	0
192	1	1	0	0	0	1	1	1	0	0
193	0	0	0	0	0			1	1	0
194	1	1	0	0	1			1	0	0
195	0	1	1	0	1			1	1	1
196								0		
197	0	1	1	0	0			1	0	0
198	1	1	0	0	1			1	0	0
199	1	1	0	0	0	1	1	1	0	0
200	0	0	1	0	0	0	0	1	1	0
201								0		
202								0		
203	1	1	0	0	0			1	0	0
204	0	0	1	1	1			1	1	0
205	0	0	1	0	0			1	1	0
206	1	0	1	0	0			1	1	0
207	1	1	0	0	1			1	1	0
208	1	0	0	1	1			1	1	0
209								0		
210	1	0	1	0	0	1	0	1	1	0
211	1	1	0	0	0	1	0	1	0	0

212 0 0 1 1 0 0 0 1 1 0

Date of Cardiac Events

CODES for all events

Dates indicate an event has occured

Blank indicates no event has occurred

Time and date of folow up is shown

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
1	15-Apr-87	11-Jul-88	453			23-Apr-87	11-Jan-88						
2	15-Apr-87	07-May-94	2579						20-Apr-87			07-May-94	
3	19-Apr-87	04-Oct-94	2725	03-Mar-94									
4	19-Apr-87	11-Jun-95	2975	09-Sep-87			09-Sep-87		13-Dec-89	24-Nov-90			
5	20-Apr-87	26-May-93	2228										
6	20-Apr-87	14-Jun-93	2247					21-Apr-87	19-Apr-89				
7	25-Apr-87	21-Mar-90	1061	28-Sep-87									
8	30-Apr-87	01-May-87	1									01-May-87	
9	03-May-87	20-Jun-90	1144			04-May-87		04-May-87	04-May-88				
10	27-May-87	22-Dec-89	940										
11	29-May-87	22-Jun-90	1120	23-Jun-89									
12	27-May-87	28-Nov-94	2742										
13	28-May-87	30-May-87	2		29-May-87	29-May-87		29-May-87				30-May-87	
14	28-May-87	26-Jun-87	29			29-May-87	10-Jun-87					26-Jun-87	
15			-1										
16	01-Jun-87	02-Nov-91	1615						20-Nov-87				
17	01-Jun-87	13-Jul-89	773										
18	30-Jun-87	02-Nov-94	2682	04-Jul-91					08-Jul-91		08-Jul-91		
19	07-Jul-87	26-Oct-94	2668			03-Sep-92							
20	25-Jan-89	04-Mar-93	1499	01-Jul-88									
21	12-Jul-87	06-Mar-90	968						12-Jan-88				06-Mar-90
22	11-Jul-87	29-Aug-87	49		04-Aug-87							29-Aug-87	
23	18-Jul-87	04-Jan-89	536										
24	02-Aug-87	14-May-90	1016	14-Sep-87							19-Oct-89		
25	10-Aug-87	17-Mar-93	2046						05-Jan-93				
26	17-Aug-87	25-Jan-88	161						18-Aug-87				

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
27	18-Aug-87	13-Dec-94	2674	23-Dec-87			04-Nov-87		25-Apr-93				
28	20-Aug-87	03-Apr-90	957		26-Aug-87					01-Nov-87			
29	21-Aug-87	18-Aug-90	1093			22-Aug-87							18-Aug-90
30	24-Aug-87	11-May-94	2452	23-Jan-91	01-Sep-91	26-Aug-87	11-Sep-88						
31	02-Nov-87	20-Jun-90	961	01-May-88	10-Nov-88						17-Jul-88		
32	03-Nov-87	24-May-91	1298	25-Nov-87	04-Nov-87					09-Feb-88			
33	11-Nov-87	15-Sep-88	309										
34	11-Nov-87	14-Nov-87	4			12-Nov-87							14-Nov-87
35	12-Nov-87	23-Feb-94	2295	25-Mar-93	14-Nov-87			15-Nov-87	16-Nov-87				
36	21-Nov-87	26-Feb-93	1924		27-Feb-89	24-Oct-92							
37	25-Nov-87	14-Nov-92	1816	13-Jan-88	07-Jun-88	25-Nov-87	23-May-90	26-Nov-89					
38	03-Dec-87	09-Aug-90	980	14-Apr-89	22-Nov-93				05-Dec-87				
39	03-Dec-87	16-Dec-92	1840	19-Feb-88			19-Feb-88		08-Dec-87	08-Dec-87			
40	07-Dec-87	09-Mar-92	1554	08-Jun-88									
41	10-Dec-87	08-Oct-92	1764			11-Dec-87	23-Dec-88	11-Dec-87					
42	16-Dec-87	09-Feb-94	2247										
43	18-Dec-87	27-Jul-88	222										
44	22-Dec-87	26-Dec-87	5					26-Dec-87	26-Dec-87			26-Dec-87	
45	29-Dec-87	06-Jul-93	2016										
46	17-Jan-88	27-Sep-88	254	23-Mar-88			22-Aug-88					27-Oct-88	
47	21-Jan-88	20-Sep-90	973	27-Jun-88		29-Jan-88	23-Dec-88						
48	27-Jan-88	26-Dec-94	2525	18-Oct-88	28-Jan-88	28-Jan-88	16-Mar-88		08-Apr-90				
49	28-Jan-88	30-Jun-89	519	29-Jan-88		29-Jan-88	25-Mar-88						30-Jun-89
50	05-Feb-88	13-Oct-93	2077				07-Mar-90	12-Dec-89					
51	07-Feb-88	14-Dec-88	311	17-Aug-88	08-Feb-88			08-Feb-88					
52	10-Feb-88	08-Jun-94	2310	15-Feb-89	18-May-89					02-Jun-89			

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
53	11-Feb-88	12-Feb-88	1			11-Feb-88		11-Feb-88				12-Feb-88	
54	12-Feb-88	08-Sep-93	2035	15-Nov-88	19-Mar-88				19-Dec-92				
55	24-Feb-88	09-Jan-91	1050										
56	29-Feb-88	12-Dec-94	2478				28-Mar-88				03-Mar-89		
57	03-Mar-88	01-May-90	789										
58	17-Mar-88	17-Feb-93	1798										
59	23-Mar-88	25-Jan-95	2499	19-Oct-88						11-Apr-89			
60	26-Mar-88	13-Feb-94	2150	14-Jul-88			14-Sep-88	27-May-88	20-Jun-89				13-Feb-94
61	27-Mar-88	01-May-88	35		22-Apr-88	27-Mar-94		27-Mar-94					01-May-88
62	29-Mar-88	20-Feb-94	2154		02-Apr-88			29-Apr-88			29-Mar-90		
63	01-Apr-88	28-Nov-94	2432		18-Oct-89						01-Mar-89		
64	25-May-88	12-Apr-90	687							29-Nov-88			
65	14-Apr-88	02-Jun-92	1510		14-Apr-88		17-Jan-90						
66	19-Apr-88	18-Jun-90	790	19-Jan-89							19-Oct-90		
67	20-Apr-88	24-Jan-92	1374	31-Aug-88	11-Jun-89			11-Jun-89			10-Jul-89		
68	27-Apr-88	27-Oct-93	2009	27-Oct-93									
69	07-May-88	21-Jun-89	410										
70	09-May-88	09-May-88	1									09-May-88	
71	11-May-88	24-May-89	378	29-Oct-88							11-Aug-89		
72	13-May-88	02-Feb-94	2091	09-Sep-88									
73	21-May-88	31-Dec-92	1685										
74	18-May-88	22-Sep-94	2318						26-Aug-93				
75	25-May-88	12-Dec-94	2392	12-Dec-88	29-May-88								
76	28-May-88	04-Apr-90	676								20-Dec-88		
77	28-May-88	02-Aug-90	796	30-Sep-88							08-Sep-89		
78	29-May-88	02-Sep-88	96										

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
79	29-May-88	30-Aug-88	93										
80	04-Jun-88	03-Apr-90	668										
81	08-Jun-88	07-Sep-88	91										
82	09-Jun-88	13-Feb-91	979	17-Aug-88									
83	15-Jun-88	01-Jul-89	381			16-Jun-88			01-Jul-88				
84	09-Jul-88	18-Apr-89	283			06-Jul-88	07-Jul-88	26-Jul-88					
85	26-Jun-88	20-Mar-90	632						28-Feb-90			20-Mar-90	
86	29-Jun-88	12-Sep-90	805	03-Aug-88	30-Jun-88								
87	30-Jun-88	11-Dec-89	529	0			21-Apr-89						
88	01-Jul-88	09-May-89	312				18-Jan-89	07-Jul-88				09-May-89	
89	10-Jul-88	17-Dec-94	2351	23-Nov-88			06-Sep-88				15-Jan-89		
90	10-Jul-88	07-Mar-89	240										
91	16-Jul-88	04-Aug-91	1114										
92	17-Jul-88	17-Jul-88	1									17-Jul-88	
93	24-Jul-88	06-Feb-92	1292	12-Aug-88	03-Aug-88			24-Jul-88		20-Oct-88			
94	25-Jul-88	07-Sep-93	1870	29-Aug-90						26-Nov-92			
95	07-Aug-88	08-Jun-94	2131						31-May-93				
96	13-Aug-88	11-Jan-95	2342	25-Jun-90			11-Oct-89						
97	19-Aug-88	24-Mar-93	1678										
98	21-Aug-88	15-May-90	632		24-Aug-88								
99	08-Sep-88	24-Jul-94	2145		12-Sep-88	13-May-89			15-Sep-88				
100	13-Sep-88	23-Jun-94	2109			01-Nov-90							
101	15-Sep-88	12-Mar-91	908	22-Nov-89		16-Sep-88					23-Jan-90		
102	20-Sep-88	03-Jan-92	1200										
103	21-Sep-88	02-Aug-90	680										
104	28-Sep-88	03-May-90	582	20-Mar-89	29-Sep-88							03-May-90	

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
105	30-Sep-88	29-Mar-89	180		30-Sep-89								
106	04-Oct-88	02-May-90	575										
107	08-Oct-88	27-Dec-89	445	02-Feb-89			02-Feb-89						
108			-1										
109	18-Oct-88	06-Sep-93	1784	26-Apr-89			26-Apr-89	19-Oct-88					
110	21-Oct-88	07-Dec-94	2238			14-Nov-88		14-Nov-88					
111	27-Oct-88	13-Mar-90	502										
112	30-Oct-88	16-Feb-90	474	22-Dec-88			22-Dec-88						
113	02-Nov-88	26-Apr-89	175										
114	06-Nov-88	03-Jan-95	2249	10-Jul-91									
115	08-Nov-88	08-Nov-88	1									08-Nov-88	
116	09-Nov-88	10-Nov-88	2									10-Nov-88	
117	13-Nov-88	18-Aug-92	1374			14-Nov-89							
118	23-Nov-88	30-Oct-91	1071		24-Nov-88				15-Sep-92			26-Oct-92	
119	24-Nov-88	26-Oct-92	1432										
120	28-Nov-88	23-Nov-94	2186	18-Jan-89	29-Nov-88		19-Feb-92						
121	08-Dec-88	23-Jan-89	46										
122	12-Dec-88	06-Oct-94	2124	24-Jan-89			24-Jan-89						
123	14-Dec-88	22-Jul-92	1316	28-Feb-90						28-Mar-90			
124	20-Dec-88	23-Sep-92	1373	29-May-91	08-Apr-90								
125	29-Dec-88	06-Jun-90	524						04-Mar-89				
126	29-Dec-88	01-Nov-91	1037										
127	29-Dec-88	07-Mar-90	433	19-Apr-89	29-Dec-88		26-Sep-89	29-Dec-88				21-Mar-90	
128	-1	-1	-1										
129	01-Apr-89	27-Apr-94	1852		22-Mar-93			12-Jan-90					
130	09-Apr-89	30-Jan-90	296			07-Apr-89							

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
131	01-Apr-89	07-Feb-90	312										
132	14-Apr-89	23-Dec-90	618										
133	16-Apr-89	29-Aug-92	1231	24-May-89									
134	17-Apr-89	06-Oct-94	1998										
135	21-Apr-89	08-Sep-94	1966	22-Nov-89			22-Nov-89		20-Feb-90				
136	27-Apr-89	03-Apr-91	706										
137	03-May-89	19-Mar-91	685										
138	06-May-89	21-Sep-94	1964	26-Jul-89							18-Sep-90		
139	21-May-89	18-Dec-91	941								02-Nov-89		
140	24-May-89	16-Mar-94	1757	12-Jul-89	25-Nov-90		15-Nov-90				01-Sep-93		
141	04-Jun-89	28-Nov-89	177		04-Jun-89								
142	05-Jun-89	11-Sep-92	1194			05-Jun-89	14-Jun-89						
143	06-Jun-89	01-Sep-94	1913								01-Sep-89		
144	08-Jun-89	14-Jan-90	220			09-Jun-89	02-Aug-89				14-Jan-90		
145	13-Jun-89	11-Oct-90	485										
146	13-Jun-89	08-Nov-92	1244										
147	17-Jun-89	29-Dec-93	1656	01-May-92					26-Aug-90		07-Jan-93		
148	17-Jun-89	02-Nov-90	503		17-Jun-89								
149	18-Jun-89	24-Sep-94	1924	22-Aug-89	17-Jun-89	19-Jun-89	01-Nov-89	20-Oct-89	20-Oct-89		01-Oct-89		
150	03-Jul-89	26-Feb-93	1334	14-Sep-90	21-Jul-90								
151	04-Jul-89	05-Dec-90	519										
152	12-Jul-89	28-Oct-89	108										
153	28-Jul-89	26-Sep-89	60										
154	07-Aug-89	18-Aug-89	11										
155	19-Jul-89	12-Sep-91	785	06-Jun-90	06-Sep-89	19-Jul-89							12-Sep-91
156	12-Aug-89	18-May-91	644	16-Apr-91	16-May-90							18-May-91	

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
157	23-Aug-89	22-Apr-92	973			23-Aug-89		24-Aug-89			18-Oct-89		
158	27-Aug-89	27-Aug-89	1									27-Aug-89	
159	04-Sep-89	03-Dec-92	1186	11-Oct-89	04-Sep-89			04-Sep-89			22-Jan-91		
160	23-Sep-89	10-Jan-92	839	21-Oct-90				23-Sep-89					
161	07-Oct-89	06-Jul-94	1733	09-May-90	08-Dec-89				26-Jun-90				
162	24-Nov-89	22-Dec-94	1854	27-Jun-90	30-Nov-89		27-Jun-90						
163	27-Nov-89	21-Jan-94	1516										
164	28-Nov-89	02-Nov-94	1800				29-Nov-89	02-Dec-89					
165	29-Nov-89	10-Jan-90	42										
166	30-Jan-89	15-May-91	835										
167	04-Dec-89	08-Dec-94	1830	30-Jan-90			30-Jan-90				01-Mar-91		
168	07-Dec-89	16-Dec-94	1835			12-Jul-90							
168	17-Dec-89	10-May-94	1605	02-Aug-91	23-Jan-90		23-Jan-90						
170	20-Dec-89	14-Dec-93	1455	17-May-90									
171	26-Dec-89	09-May-90	134										
172	19-Jan-90	23-May-94	1585	23-Mar-91	26-Sep-93								
173	19-Jan-90	22-Oct-93	1372	28-Feb-90			05-Sep-90		11-Sep-90				
174	22-Jan-90	12-Dec-90	324					23-Jan-90					
175	02-Feb-90	15-Aug-93	1290	10-Feb-92	26-Jun-93								
176	05-Feb-90	13-Oct-94	1711	17-Dec-89	05-Mar-91	05-Feb-90					06-Aug-92	17-Jan-95	
177	11-Feb-90	10-Aug-92	911	20-Mar-92	11-Feb-90								
178	14-Feb-90	08-Oct-92	967	12-Feb-91									
179	15-Feb-90	22-Apr-94	1527	13-Feb-92		17-Feb-90	13-Feb-92						
180	17-Feb-90	13-Jul-94	1607	19-Dec-90			19-Dec-90				25-Feb-90		
181	26-Feb-90	30-Nov-94	1738										
182	05-Mar-90	19-Jun-91	471	19-Dec-90									

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
183	13-Mar-91	28-Sep-94	1295										
184	19-Mar-91	12-Oct-93	938		05-Oct-93				23-Mar-91				
185	23-Mar-91	27-Jan-94	1041			25-Mar-91							
186	26-Mar-91	09-Nov-92	594										
187	29-Mar-91	04-Jan-95	1377		01-Sep-95								
188	14-Apr-91	28-Jun-92	441										
189	24-Apr-91	31-Aug-93	860	10-Jan-92									
190	26-Apr-91	06-Oct-94	1259	22-May-91	10-May-91		25-Sep-91						
191	06-May-91	28-May-92	388			09-May-91							
192	13-May-91	12-Jan-94	975										
193	15-May-91	12-Aug-92	455										
194	17-May-91	08-Jul-91	52						08-Jul-91				
195	-1	-1	-1										
196	27-May-91	04-Jun-91	8			31-May-91						04-Jun-91	
197	29-May-91	18-Apr-94	1055			31-May-91							
198	30-May-91	01-Apr-92	307										
199	11-Jun-91	20-Aug-93	801										
200	15-Jun-91	28-Apr-94	1048										
201	16-Jun-91	26-Jun-91	11			19-Jun-91		17-Jun-91	18-Jun-91			26-Jun-91	
202	16-Jun-91	09-Nov-94	1242	17-Oct-91	17-Jun-91	17-Jun-91							
203	29-Jun-91	14-Aug-91	46										
204	30-Jun-91	12-Aug-93	774	01-Mar-92									
205	01-Jul-91	15-Nov-93	868										
206	04-Jul-91	16-Jun-94	1078	01-Oct-91	20-Jan-92						01-Nov-93		
207	28-Jul-91	16-Dec-92	507										

Patient NO	Admission Date	Follow up Date	Time Days	Angina	Unstable Angina	PeriInfarct ALVF	Outpatient CCF	Further MI	PTCA	CABG	Arrythmia	Cardiac Death	Non Cardiac Death
208	09-Aug-91	10-Oct-94	1158	29-Jul-92	14-Aug-91		06-May-92						
209	20-Aug-91	20-Aug-91	1			21-Sep-91						21-Aug-91	
210	25-Sep-91	16-Sep-92	357			25-Sep-91							
211	13-Oct-91	19-May-93	584					13-Oct-91					
212	16-Oct-91	21-Apr-94	918			22-Oct-91							

SCIENTIFIC PRESENTATIONS OF RESEARCH

1. Predischarge exercise testing and coronary patency following thrombolytic therapy for acute myocardial infarction.
P.D. MacIntyre**, J.D. Gemmill*, K.J. Hogg*, F.G. Dunn*, A.P. Rae*, W.S. Hillis**
Departments of Cardiology, Western Infirmary** and Stobhill Hospital*
Scottish Society for Experimental Medicine, Dundee, 1992 (Oral Presentation).

2. Predischarge exercise testing in the prediction of vessel disease following thrombolysis for acute myocardial infarction.
P.D. MacIntyre**, J.D. Gemmill*, K.J. Hogg*, F.G. Dunn*, A.P. Rae*, W.S. Hillis**
Departments of Cardiology, Western Infirmary** and Stobhill Hospital*
British Cardiac Society, May 1995. (Oral Presentation).

3. Predischarge exercise testing in the prediction of coronary patency following thrombolysis for acute myocardial infarction.
P.D. MacIntyre**, J.D. Gemmill*, K.J. Hogg*, F.G. Dunn*, A.P. Rae*, W.S. Hillis**
Departments of Cardiology, Western Infirmary** and Stobhill Hospital*
European Cardiac Society August 1995 (Poster Presentation).

4. Pre discharge exercise testiing in the prediction of cardiac events over 5 years following thrombolysis for acute myocardial infarction.
P.D. MacIntyre**, J.D. Gemmill*, K.J. Hogg*, F.G. Dunn*, A.P. Rae*, W.S. Hillis**
Departments of Cardiology, Western Infirmary** and Stobhill Hospital*
Bitish Cardiac Society 1996 (Poster Presentation).

5. Pre discharge exercise testiing in the prediction of cardiac events over 5 years following thrombolysis for acute myocardial infarction.
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Departments of Cardiology, Western Infirmary** and Stobhill Hospital*
European Cardiac Society 1996 (Poster Presentation).